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ORIGINAL ARTICLES.

THE DISAPPEARANCE OF INTRAVENOUSLY INJECTED  
LYMPHOCYTES IN THE ABSENCE OF THE GASTRO-  
INTESTINAL TRACT.

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Cincinnati, Ohio.)

It is generally concluded that old or worn-out and transfused erythrocytes may leave the circulating blood by either of two mechanisms; phagocytosis by the reticulo-endothelial system<sup>2,3,18</sup> or cellular fragmentation and subsequent lysis.<sup>19,20,25</sup> Granulocytes and monocytes also may be removed by these mechanisms. But, beside phagocytosis and autolysis<sup>5,8,15,17</sup> two additional explanations for the disappearance of lymphocytes have been suggested, viz., differentiation into red blood cells<sup>11,12</sup> and excretion into the lumen of the gastro-intestinal tract.<sup>1,10,24</sup> The present study reveals that the gastro-intestinal tract plays only a minor rôle, if any, in the elimination of lymphocytes from the general circulation.

**Methods and Materials.** New Zealand Red rabbits, which weighed approximately 1500 gm. each, were used. All blood determinations were made by the use of standardized techniques and equipment. Sodium amytal, the administration of which is followed by a peripheral leukopenia<sup>9</sup> (Table 1), but only a mild lymphopenia, was selected as the anesthetic of choice.

Viable lymphocytes were obtained by removing and suspending, in saline, the cells of the submucosa of rabbit appendices which were secured surgically. Triple washing in saline was necessary to remove tissue fibrinogen. Five per cent of the cells were monocytes and clasmotocytes and 95% were lymphocytes (50%-60% young, 30%-40% mature, and 10% old forms—Wiseman criteria<sup>26b</sup>). The total number of lymphocytes varied from 100 million to 3 billion in different appendices.

Gastro-enterectomy was performed through a large midline abdominal incision by the double ligation and severance of the rectum, inferior and superior mesenteric vessels, celiac axis, esophagus and portal vessels which permitted the removal of the stomach, spleen, pancreas, mesenteric lymph nodes, duodenum, small intestines, colon and sigmoid in one mass. The



kidneys remained intact. As soon as the effects of the anesthesia wear off, gastro-enterectomized rabbits jump and hop about quite normally and will live from 8 to occasionally 24 hours.

TABLE 1.—EFFECT OF AMYTAL ON LEUKOCYTE COUNT.

The total leukocyte counts (expressed in hundreds per c.mm.) of 6 rabbits made before and after the intravenous injection of 50 mg. of sodium amytal per kilo of body weight are listed below. In 5 rabbits the anesthetic was administered on 4 occasions, each administration 24 hours apart. Hemoglobin estimations also were made but no significant changes occurred.

Rabbit No.	Anesthesia.	Pre-injection.	15 min. post-inj.	30 min. post-inj.	1 hr. post-inj.	2 hrs. post-inj.
27	First	92	78	86	45	39
	Second	87	..	86	50	60
	Third	101	..	50	58	45
	Fourth	96	54	46	65	80
28	First	71	..	44	50	58
	Second	82	..	62	68	72
	Third	94	82	..	62	61
	Fourth	88	..	81	60	70
29	First	74	61	46	81	121
	Second	92	..	50	78	92
	Third	89	71	39	41	78
	Fourth	99	78	82	72	112
30	First	81	..	33	50	66
	Second	82	..	52	70	69
	Third	53	54	41	35	91
	Fourth	74	40	86	90	
26	First	75	52	40	51	72
	Second	90	..	44	52	76
	Third	66	..	50	..	91
	Fourth	78	..	45	80	90
14	First	94	80	60	68	102
Averages . . . . .		83.2	65.8	61.1	65.3	77.2

**Experiments and Results.** *Experiment 1 (Table 1).* Five normal rabbits were injected intravenously with sodium amytal (50. mg. per kilo) every day for 4 days, inducing a deep anesthesia of approximately 2 hours' duration. An additional rabbit was given a single injection. Total leukocyte counts and hemoglobin estimations were made before, 15 and 30 minutes, 1 and 2 hours, after the administration of the drug. There were no significant changes in the estimations of hemoglobin and the depression of the leukocyte levels following anesthesia was slight and of about 2 hours' duration. No change of a permanent character was noted in the numbers of circulating white blood cells during the 4-day period. In fact, in most instances the leukopenia after the fourth induction of anesthesia was less severe than that after the first.

*Experiment 2 (Table 2 and Chart 1).* Table 2 illustrates the recorded estimation of the blood levels before and after amyotalization, splenectomy and gastro-enterectomy of 5 litter mates. Each procedure was separated by a period of 24 hours. In 2 rabbits (Nos. 46 and 50) there was a decrease of, in one (No. 49) there was an elevation of, and in 2 (Nos. 51 and 55) no change of the absolute numbers of lymphocytes, 5 hours after the induction of the anesthesia. Five hours after splenectomy the levels of the blood of each rabbit had returned essentially to those noted preoperatively. But 5 hours after gastro-enterectomy a severe lymphopenia became evident, and the low level persisted until death in spite of the fact that 3 of the 4 rabbits developed a leukocytosis.

TABLE 2.—LYMPHOCYTES AFTER AMYTALIZATION, SPLENECTOMY AND GASTRO-ENTERECTOMY.

The absolute numbers of lymphocytes, the percentages of lymphocytes and the total number of white blood cells (expressed in hundreds per c.mm.) of 5 rabbits which were first amytalized, and after a 24-hr. period were amytalized and splenectomized, and finally after a second 24-hr. period 4 were amytalized and gastro-enterectomized. Hemoglobin estimations were made simultaneously with each differential, but the changes were insignificant.

		← 2½ hrs. → Amytal and splenectomy.					← 24 hrs. → Amytal and gastro-enterectomy.														
		30 min.					1 hr.					1 hr.					15-19 hrs.				
		Pre- anes- thesia. post- anes- thesia.					Pre- anes- thesia. post- anes- thesia.					Pre- anes- thesia. post- anes- thesia.					Pre- anes- thesia. post- anes- thesia.				
		1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.				
		1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.				
		1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.				
		1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.				
		1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.				
		1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.				
		1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.				
		1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.					1 hr. 3 hrs. 5 hrs.				
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Chart 1 illustrates the persistent lymphopenia which followed the gastro-enterectomy of 8 additional rabbits. Six of the 8 developed a terminal leukocytosis.

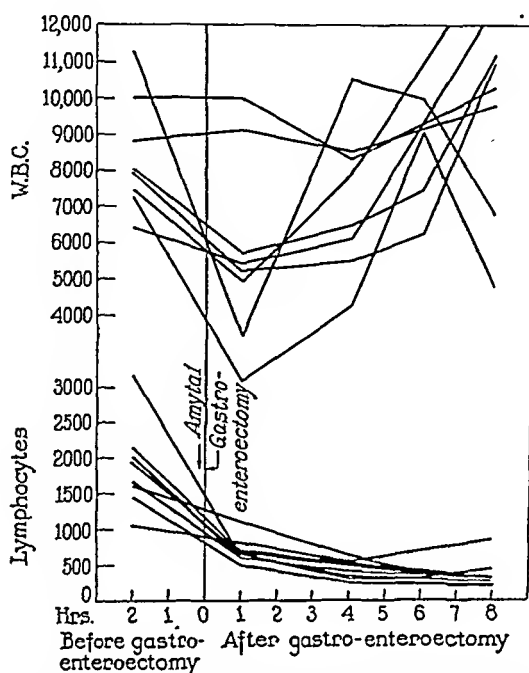


CHART 1.—The number of leukocytes (per c.mm.) and the absolute numbers of lymphocytes (per c.mm.) in the peripheral circulation of 8 rabbits before and after gastro-enterectomy.

*Experiment 3 (Table 3).* In 2 gastro-enterectomized rabbits (Nos. 43 and 44) the peripheral lymph nodes, viz., the axillary, inguinal and popliteal, were removed. By examining Table 3, it can be observed that there was no essential difference in blood levels of these rabbits and those of Experiment 2. And it may be assumed that the peripheral lymph nodes produced few circulating lymphocytes.

TABLE 3.—EFFECT OF GASTRO-ENTERECTOMY AND LYMPHADENECTOMY ON LYMPHOCYTE LEVELS.

The table illustrates the absolute numbers and percentages of lymphocytes, the total numbers of white blood cells (expressed in hundreds per c.mm.) and the percentage of hemoglobin, at preoperative and postoperative intervals, of 2 rabbits from which the stomach, small and large intestines, spleen and mesenteric, popliteal, inguinal and axillary lymph nodes had been removed.

Rabbit No.	Lymphocytes, W. B. C. and hemoglobin.	Preop.	1 hr. postop.	4 hrs. postop.	6 hrs. postop.	8 hrs. postop.	9 hrs. postop.
43	Absolute No.	30	11	9	..	0.6	
	Per cent	60	50	16	..	2	
	Total W. B. C.	50	23	55	..	36	
	Hemoglobin (%)	94	96	84	..	92	
44	Absolute No.	10	10	6	2	1	2
	Per cent	20	28	11	3	4	5
	Total W. B. C.	52	38	63	70	47	40
	Hemoglobin (%)	100	91	83	94	91	104

*Experiment 4 (Chart 2).* This experiment was performed to demonstrate the changes in the number of circulating leukocytes and lymphocytes of normal rabbits which received intravenous injections of heterogenetic lymphocytes. Normal rabbits weighing 1500 gm. contain about 100 cc. of blood, and intravenous injections of normal lymphocytes should raise the total number of circulating white blood cells correspondingly.

As is illustrated, Rabbit 65 was given intravenously 192 million lymphocytes suspended in 10 cc. of saline, and Rabbit 66, 332 million (Chart 2). The total number of leukocytes decreased immediately after the injections in both animals, and a return to the former normal levels did not occur until after a period of 2 to 3 hours had elapsed. There was a slight but temporary elevation in the number of circulating lymphocytes, followed by a compensatory depression and then a gradual return to the original normal levels all within 6 hours. It is apparent therefore that only a relative lymphocytosis existed very temporarily after the introduction of viable lymphocytes into these normal rabbits.

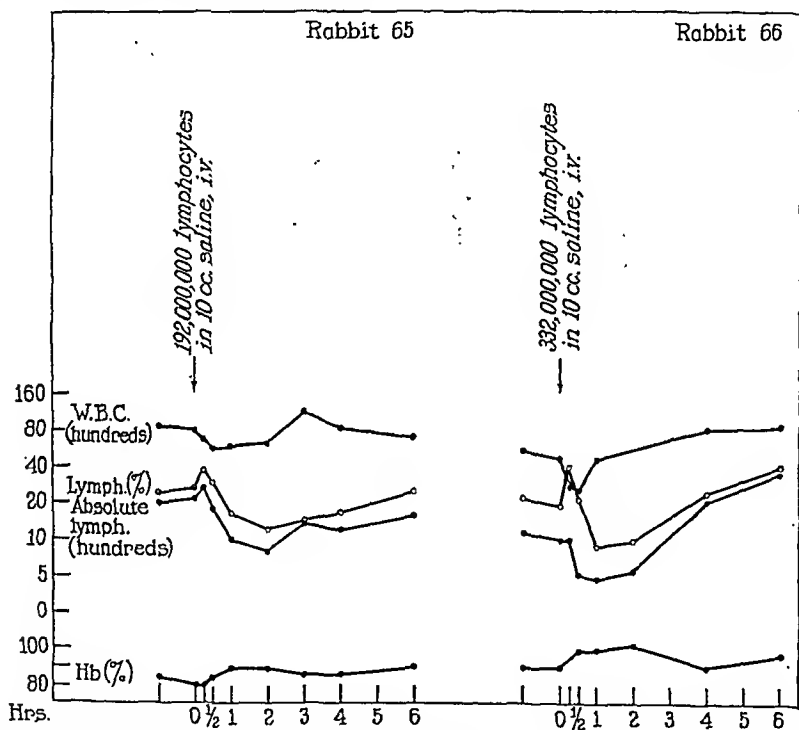


CHART 2.—Changes in the leukocyte, lymphocyte and hemoglobin levels of 2 rabbits after the intravenous administration of viable lymphocytes.

In no respect did these animals develop abnormal reactions to the injection.

*Experiment 5 (Charts 3-6).* If the gastro-intestinal tract is the site of lymphocyte excretion, the intravenous injection of lymphocytes into the circulating blood of rabbits, from which the gastro-intestinal tract has been removed, should be followed by an elevation, and a maintenance of the elevation, of the number of these circulating cells. The results of the experiment are described in four parts.

*Chart 3.* Blood examinations were made before and at irregular intervals after gastro-enterectomy until death of Rabbit 59. As illustrated, the percentage and absolute number of lymphocytes declined sharply after

gastro-enterectomy. Three and one-half hours after the operation the percentage of lymphocytes was 7 and the absolute number 400. At this time 10 million autogenetic lymphocytes which had been suspended in 10 cc. of saline were given intravenously. The injection was followed by no significant change in the levels of the blood cells. One hour and 45 minutes later, long after any influence that the first injection may have had on the lymphocyte level, 2 billion 600 million heterogenetic lymphocytes suspended in 10 cc. of saline were administered intravenously. Fifteen minutes after this injection the percentage of lymphocytes increased to 17.5 and the absolute number to 700. However, within  $3\frac{1}{2}$  hours the percentage had returned to the former level of 5 and the absolute number to 400. At

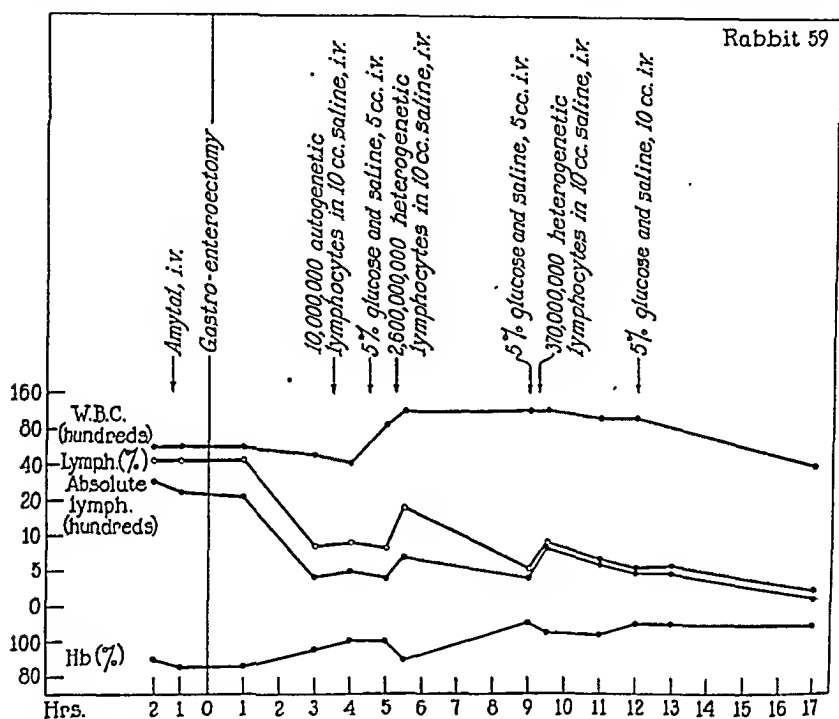


CHART 3.—Changes in the lymphocyte, leukocyte and hemoglobin levels of Rabbit 59 after gastro-enterectomy and after the intravenous administration of viable lymphocytes.

that time, a third injection of 370 million heterogenetic lymphocytes was given intravenously. The elevation in the numbers of circulating lymphocytes following the injection was slight and insignificant. The animal died 17 hours after gastro-enterectomy with the total leukocyte level within the normal range but with a severe lymphopenia—the absolute number being 150. In this gastro-enterectomized animal, intravenously administered autogenetic and heterogenetic lymphocytes disappeared rapidly from the blood stream.

The behavior of the animal was not unusual at any time. After the effects of the anesthetic had worn off the animal jumped and hopped about normally until after the third injection of cells. A prone position was then assumed. The rabbit did not lose its sense of balance until 1 hour before death.

The body temperature was maintained at a normal level by the use of electric lamps.

Chart 4 illustrates the findings of Rabbit 62. The leukocyte and lymphocyte levels were followed before and after administration of amytal, splenectomy and gastro-enterectomy. One and a half hours after the latter operation 2 billion, 230 million autogenetic lymphocytes were administered intravenously. The leukocyte count before was 10,500, but 15 minutes after the injection was 1550. The percentage of lymphocytes increased from 6.5% before to 25% after and the absolute number from 550 to 1000. Within 2 hours the levels approximated those present immediately previous to injection. Just before death, 11 hours after gastro-enterectomy, leukocyte count was 6000; the percentage of lymphocytes was 7.5 and the absolute number was 500.

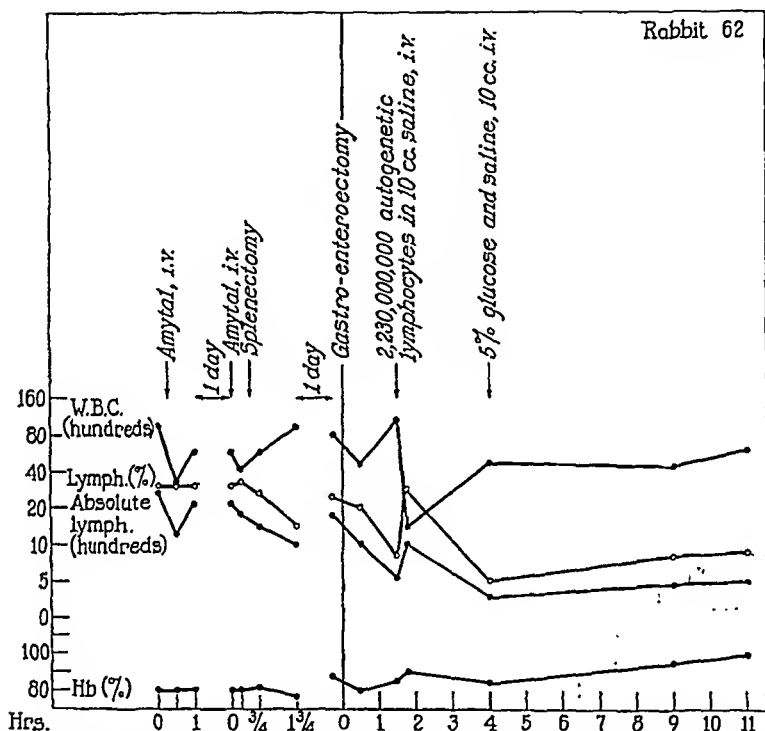


CHART 4.—Changes that occurred in the leukocyte, lymphocyte and hemoglobin levels of Rabbit 62 after each of the following: anesthesia, splenectomy, gastro-enterectomy and the intravenous injection of viable autogenetic lymphocytes.

The gradual elevation of the percentage of hemoglobin previous to death might well be a result of dehydration because urine was excreted in large quantities during the entire experiment.

The behavior of this animal was similar to that of the first rabbit.

Chart 5 illustrates the hematologic findings of Rabbit 64, which was first amytalized, 24 hours later splenectomized and then after another interval of 24 hours was gastro-enterectomized. Following the latter operation, the decline of the number of circulating lymphocytes was gradual and of a permanent nature. After an injection of 201 million autogenetic lymphocytes, the rate of the decline was temporarily decreased. But by the third hour after injection the absolute number of lymphocytes had decreased to the low level of 400. This level was maintained until death, 15 hours later.

The hemoglobin level did not vary significantly during the period from splenectomy until death.

Chart 6 illustrates the changes of the leukocyte and lymphocyte levels of Rabbit 61, to which lymphocytes were administered both before and after gastro-enterectomy. The intact animal was given intravenously 168 million heterogenetic lymphocytes. An increase occurred in the number of leukocytes from 7100 before to 9500 three hours after the injection, but the percentage of lymphocytes declined from 24 to 10, and the absolute number from 1650 to 950. Two days later the percentage of

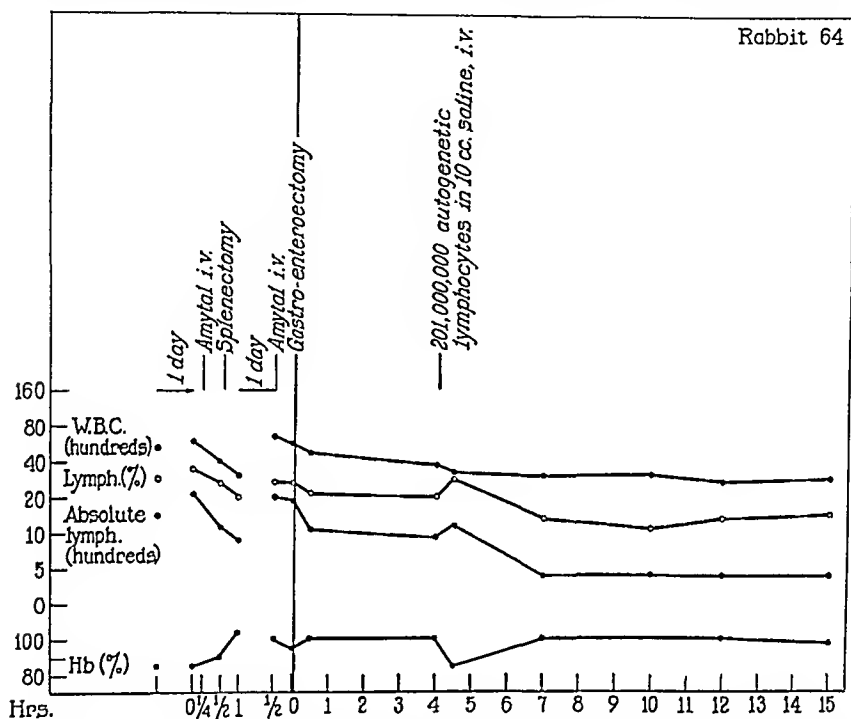


CHART 5.—Changes in the leukocyte, lymphocyte and hemoglobin levels of Rabbit 64 after each of the following: splenectomy, gastro-enterectomy and the intravenous injection of viable autogenous lymphocytes.

lymphocytes rose to 40% and the absolute number to 2000. Immediately following splenectomy the anticipated temporary decline in the number of leukocytes and lymphocytes occurred. Twenty-four hours later the levels, however, were essentially the same as those present at the time of the injection of lymphocytes, 72 hours earlier. Gastro-enterectomy was then performed, and the usual lymphopenia developed. Three hours after the operation 200 million autogenous lymphocytes were administered intravenously. There was a sharp rise in the percentage and absolute number of lymphocytes following the injection. The percentage before was 15 but 15 minutes after the injection 34; the absolute number before was 550, and after, 800. However, the leukocyte level remained very constant at about 3500 during the 2-hour period, but later it increased gradually and reached a peak of 14,000 at the time of death 17 hours after gastro-enterectomy and 14 hours after the second injection of lymphocytes. During the last 12 hours of the rabbit's life, the absolute number of lymphocytes remained below 500. This rabbit destroyed intravenously administered lymphocytes as rapidly after the removal of the intestines as before.

The essential postmortem findings of the 4 rabbits used in Experiment 5 were: diffuse congestion of the lungs, edema of the myocardium, toxic nephritis, acute degenerative hepatitis, normally hyperplastic bone marrow and small hemorrhages in the cervical and axillary lymph nodes. The popliteal nodes were hypoplastic. No accumulation of lymphocytes was observed in any of the tissues examined.

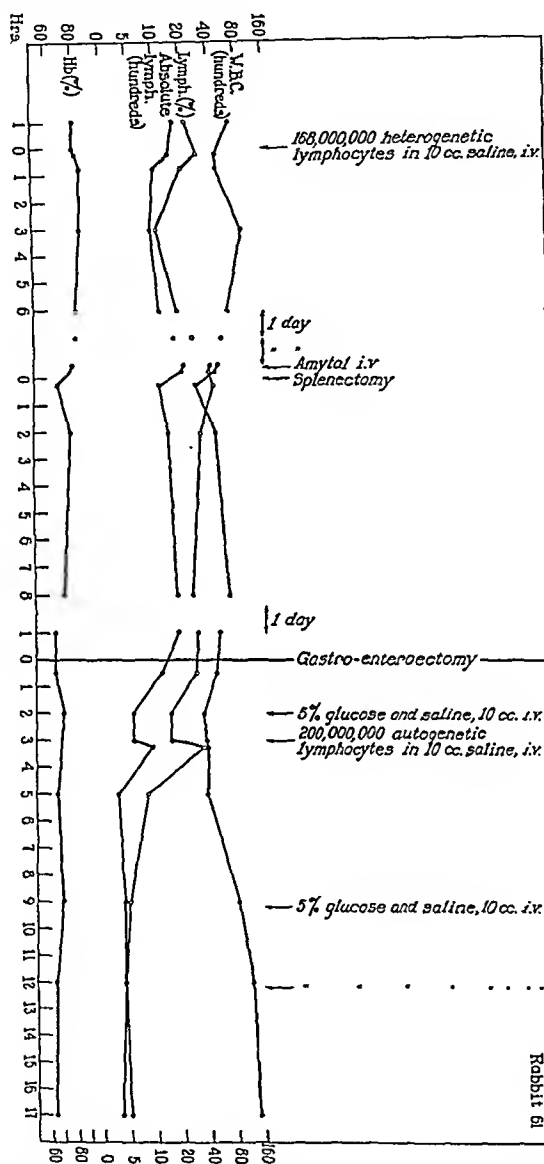


CHART 6.—Changes in the leukocyte, lymphocyte and hemoglobin levels of Rabbit 61 after each of the following: intravenous injection of heterogenetic lymphocytes before surgical alterations, splenectomy, gastro-enterectomy and the intravenous administration of autogenous lymphocytes after gastro-enterectomy.

**Discussion.** The mechanisms responsible for the destruction of normal tissue and blood cells, which are constantly being replaced, are poorly understood. It is apparent that the process of lysis is an



important factor in the destruction of malignant cells in susceptible animals made immune to experimental cancer<sup>7,15</sup> and leukemia.<sup>16</sup> The results of the experiments presented above are not in opposition to similar suppositions in relation to normal cells.

The evidence that severe and persistent lymphopenia occurs immediately following gastro-enterectomy favors the hypothesis that many if not the majority of circulating lymphocytes reach the blood stream from some portion of the gastro-intestinal tract, presumably the lymphoid tissue of the submucosal layer. (Drugs,<sup>23</sup> infections, irradiations, bodily temperature changes,<sup>26a</sup> emotions,<sup>6</sup> anesthesia<sup>9,27b</sup> and normal rhythmicity<sup>21</sup> may occasionally be responsible for decreases in the absolute number of circulating lymphocytes.) The fact that tremendous numbers of lymphocytes are present in the lymph of the thoracic duct of man and animals has led many observers<sup>1,13,14,26a,27a,28</sup> previously to draw this conclusion. Yoffey and Drinker<sup>28,4</sup> state that one out of every 30 lymphocytes entering the blood stream comes from the tissue spaces, which may well explain the presence of the lymphocytes that persisted until death of the animals described herein. In 2 chickens Scott and Cook<sup>22</sup> noted a selective decrease in the number of circulating lymphocytes following large feedings of radioactive phosphorus. After the deposition of the radio-phosphorus in the bones, it became selectively destructive to the myeloid cells. Such selectivity ultimately may be important in the therapy of leukemia.

With the exception of leukemia (if leukemia is a neoplasm) neoplastic metastases rarely occur in the submucosa of the gastro-intestinal tract, a fact that the proponents of the theory that lymphocytes are the defense agents against cancer do not emphasize.

The results of the above experiments also provide evidence that not all of the lymphocytes are discarded through the gastro-intestinal mucosa. The fate of the huge numbers of lymphocytes that were injected into the animals is unknown, but they were not excreted through intestinal mucosa and they were not phagocytized by the reticulo-endothelial system since the majority of both were removed. And the reticulum cells of the bone marrow, examined microscopically, were not actively phagocytic. Presumably lysis played a predominant rôle.

**Conclusions.** 1. Many circulating lymphocytes in rabbits take origin from some portion of the gastro-intestinal tract, presumably the submucosal lymphoid layer.

2. A severe and persistent lymphopenia occurred within 2 hours following the removal of the stomach and intestines of 18 rabbits.

3. Viable lymphocytes, either autogenetic or heterogenetic administered intravenously to either normal or gastro-enterectomized rabbits disappear very rapidly from the circulating blood.

4. Excretion of lymphocytes through the mucosa of the stomach and intestines is not the only mechanism responsible for lymphocyte destruction.

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## THE ANTIANEMIC PRINCIPLE IN THE HUMAN LIVER IN CARCINOMAS OF THE STOMACH AND CECUM.

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THE relationship between gastric secretion and hematopoiesis was first established by Castle.<sup>2</sup> Sturgis and Isaacs<sup>12</sup> and Sharp,<sup>11</sup> by their successful treatment of pernicious anemia with desiccated whole hog stomach, added further evidence that this organ produces an active hematopoietic principle. Castle,<sup>3</sup> on the basis of a long series of experiments performed by himself and his associates, concluded that an "intrinsic factor" present in the normal gastric juice interacts with an "extrinsic factor" present in food to produce an antianemic principle. Although there is general agreement that this principle is formed by the stomach and stored in the liver, considerable controversy has arisen concerning its production and nature.<sup>6,10</sup>

Bence,<sup>1</sup> like Goodman and his associates,<sup>5</sup> found that after total gastrectomy the antianemic principle of hog's liver was depleted. Henning and Brugsch<sup>7</sup> observed that the most active antianemic effect is obtained from the mucosa of the pyloric antrum and their observation was confirmed by Meulengracht,<sup>9</sup> who advanced the opinion that Brunner's glands in the submucosa of the duodenum might also be the source of the antianemic principle.

Goldhamer<sup>4</sup> demonstrated the absence of the "intrinsic factor" in the gastric juice of a patient who had a macrocytic anemia and who was shown by roentgenologic examination to have a scirrhus carcinoma of the stomach. Ventriculin was used as a control therapy. In view of this observation it was of interest to test the antianemic potency of the livers of patients with carcinomas which had destroyed various portions of the gastro-intestinal tract.

**Materials and Methods**—Tests were made of the antianemic potency of extracts prepared from the livers of 2 patients who died of carcinoma of the stomach and from the liver of a third patient who died of carcinoma of the cecum. In the first case of gastric carcinoma the neoplasm involved all of the pyloric and prepyloric regions; in the second case, all of the stomach except a portion of the pars pylorica was involved. The potency of the extract of the liver of a markedly anemic and emaciated patient with carcinoma of the cecum was tested to ascertain whether the hepatic antianemic principle would be depleted in a subject with an intestinal neoplasm but no gastric lesion. As control therapy either commercial liver extract (Lilly) was used, or an extract prepared from the liver of a patient who died of cerebral hemorrhage but whose gastro-intestinal tract was normal.

The postmortem examinations were performed between 1 and 2 hours after death. The livers thus secured were kept in an electric refrigerator at a temperature of 4° C. for periods varying from 48 to 120 hours before the extracts were manufactured, and the liver from which the control extract was made was kept in the refrigerator for the same period of time.

The liver extracts were made according to the Lilly method (Sol. Liver Extr.—Lilly, N.N.R., 1937, p. 320) as follows:

After the livers had been thoroughly ground in a meat grinder, approximately 4 times their weight in distilled water was added to them. The reaction, with the aid of a glass electrode, was adjusted to a pH of between 5 and 6 by the addition of a sufficient amount of concentrated HCl. The mixture was heated to approximately 80° C., stirred at that temperature for 30 minutes, and filtered. After the precipitated proteins had been allowed to settle, the supernatant fluid was decanted and was filtered through a fast filter paper, onto which the residue was finally poured. The clear filtrate was reduced in a vacuum to a small volume (200 to 500 cc.) and sufficient alcohol was added to bring the concentration to 70% of alcohol. The solution was placed in the refrigerator overnight (at 4° C.) and the resulting precipitate was separated by filtration and discarded. The filtrate was reduced to a syrupy consistency by vacuum distillation and the residual solution was then added to 25 volumes of 95% alcohol. The solution was again placed in the refrigerator overnight and the precipitated material was recovered by decantation and subsequent centrifugalization of the residue. The precipitated material was dissolved in physiological saline (Experiment 1) and in an aqueous 1 to 10,000 merthiolate solution (Experiments 2 to 4), 1 cc. of solvent being used for each 9 to 15 gm. of the original liver. The resulting solution of liver extract was

centrifugalized at about 3300 revolutions per minute and then sterilized by filtration through a Seitz filter. After filtrations the extracts were cultured and found to be sterile. When they were injected intravenously into anesthetized dogs there were no significant pressor or depressor effects.\* When the extracts were stored in the refrigerator before use a fine precipitate appeared, but it readily dissolved at room temperature. This precipitate can be discarded without any material loss of the antianemic principle.<sup>8</sup>

EXPERIMENT 1.—*Extract from the liver of a patient with scirrhus carcinoma of the pyloric and prepyloric regions (A-38-851).* The patient was a colored female of 57, who had complained for 2 years of sore mouth, epigastric pain, vomiting of dark-colored material after meals, and gradual loss of weight. She died of bronchopneumonia shortly after admission to the hospital, before a complete hematologic study could be made. The necropsy, which was performed an hour after death, revealed a scirrhus carcinoma involving the entire pyloric and prepyloric regions of the stomach. Histologic study showed that the mucosa of these regions had been entirely replaced by the neoplastic growth. The mucosa of the remainder of the stomach was normal and there was no evidence of visceral metastasis.

The patient used for the determination of the antianemic principle was a white male of 54 who had a typical Addisonian pernicious anemia in relapse, with nervous symptoms. Hematologic examination revealed 1,740,000 red cells and 4800 white cells per c.mm. The hemoglobin value (Hellige) was 7.8 gm. (56%). The mean corpuscular volume was 132 cu. microns and the mean corpuscular hemoglobin 45 micromicrograms. The percentage of reticulocytes was 1.1. Achlorhydria was persistent following the administration of histamine.

The intramuscular injection in 3 doses of 9 cc. of liver extract (representing 126 gm. of whole liver) failed to produce an increase in the reticulocyte count over a period of 9 days. On the tenth day 9 cc. of the control extract (representing 135 gm. of whole liver) from the patient with cerebral hemorrhage was administered intramuscularly in a single dose. Within 24 hours an elevation occurred in the number of reticulocytes, which reached a peak of 22% on the sixth day following. By the eleventh day the number of red blood cells had increased to 2,650,000 and the hemoglobin value had increased to 11.3 gm. (78%) (Hellige). The total period of observation covered 20 days (Chart 1).

EXPERIMENT 2.—*Extract from the liver of a patient with scirrhus carcinoma of the stomach not involving the pyloric region (A-39-205).* The patient was a markedly emaciated white male of 62 who had complained of gradually increasing epigastric pain and progressive loss of weight over a period of several months. Hematologic examination revealed 4,000,000 red cells and 10,850 white cells per c.mm. The necropsy, which was performed 2 hours after death, revealed a scirrhus carcinoma involving the entire stomach wall except for a circular area 3 cm. in width just proximal to the pyloric ring. The lower 3 cm. of the esophagus was also involved in the neoplastic growth. Two metastatic nodules, each 1 cm. in diameter, were present in the liver and metastasis had occurred to the regional lymph nodes. Peritoneal carcinomatosis was also present. Histologic examination of the grossly uninvolved pyloric area revealed normal mucosa and no evidence of neoplastic tissue. Examination of the remainder of the stomach showed involvement of all coats except for occasional areas in which small amounts of partially atrophic mucosa remained.

The patient used for the determination of the antianemic principle in the liver was a white female of 65 with a macrocytic hyperchromic anemia.

\* These tests were kindly performed by Dr. A. G. Eaton of the Department of Physiology.

She had had severe diarrhea. Hematologic examination revealed 1,200,000 red cells and 5000 white cells per c.mm. The hemoglobin value (Hellige) was 4.6 gm. (31%). The mean corpuscular volume was 133 eu. microns and the mean corpuscular hemoglobin 38 micromicrograms. The percentage of reticulocytes was 1. The free hydrochloric acid content of the gastric secretion was 33-60 before the administration of histamine and 42-80 afterward. Bone marrow puncture revealed numerous megaloblasts.

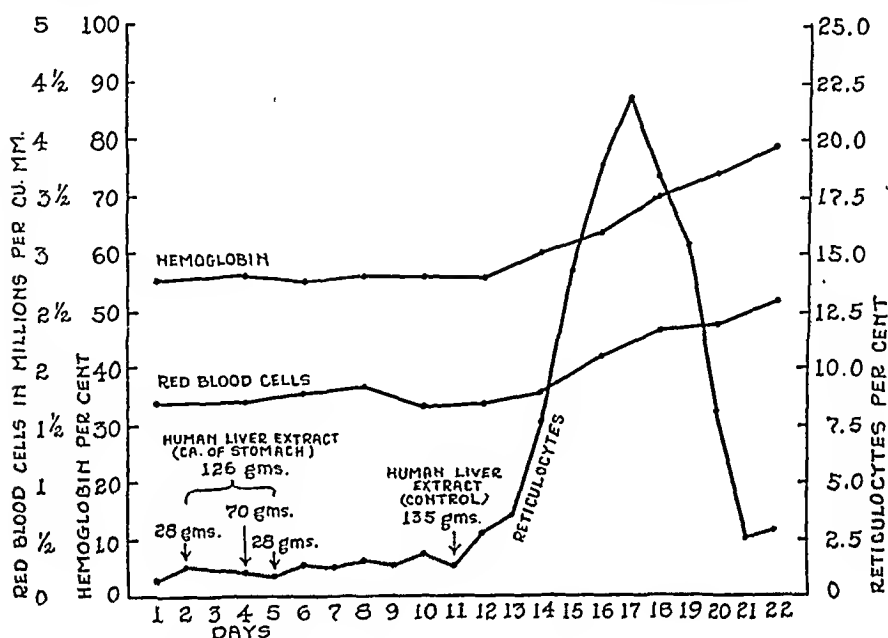


CHART 1.—The failure of response to human liver extract from a case of scirrhus carcinoma of the pyloric and prepyloric portions of the stomach.

The intramuscular injection in a single dose of 12 cc. of liver extract (representing 126 gm. of whole liver) produced a marked reticulocyte response which reached a maximum of 20% on the eighth day following (Chart 2). The patient responded well to subsequent administrations of commercial liver extract.

EXPERIMENT 3.—In order to confirm the observations regarding the content of the antianemic principle of liver extracts prepared in Experiments 1 and 2, another untreated patient with typical Addisonian pernicious anemia in relapse was treated with them. This patient, a white male of 52, had 1,220,000 red blood cells and 5600 white blood cells per c.mm. The hemoglobin value (Hellige) was 5.1 gm. (36%). The mean corpuscular volume was 114 eu. microns and the mean corpuscular hemoglobin 42 micromicrograms. The average percentage of reticulocytes was 0.7. Achlorhydria was persistent following the administration of histamine. Bone marrow puncture revealed numerous megaloblasts.

The intramuscular injection in a single dose of 10 cc. of liver extract (representing 140 gm. of whole liver) from the patient with scirrhus carcinoma of the pylorus (Experiment 1) failed to produce any reticulocytic stimulation during 11 days of observation (Chart 3). The intramuscular injection of 12.5 cc. of liver extract (representing 131.3 gm. of whole liver) from the patient with carcinoma of the stomach which did not involve the pylorus (Experiment 2) produced a significant reticulocyte response within 7 days (Chart 3).

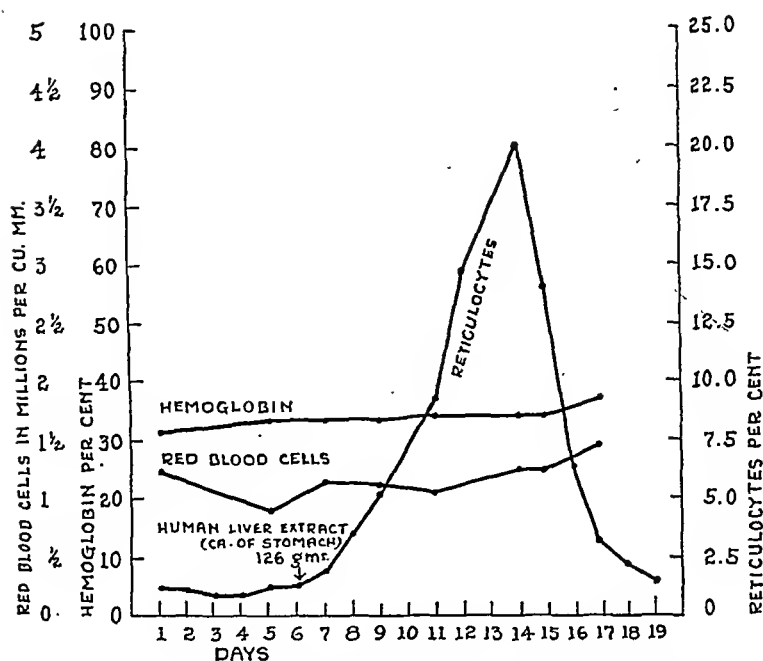


CHART 2.—The response to human liver extract from a case of scirrhus carcinoma of the stomach not involving the pyloric region.

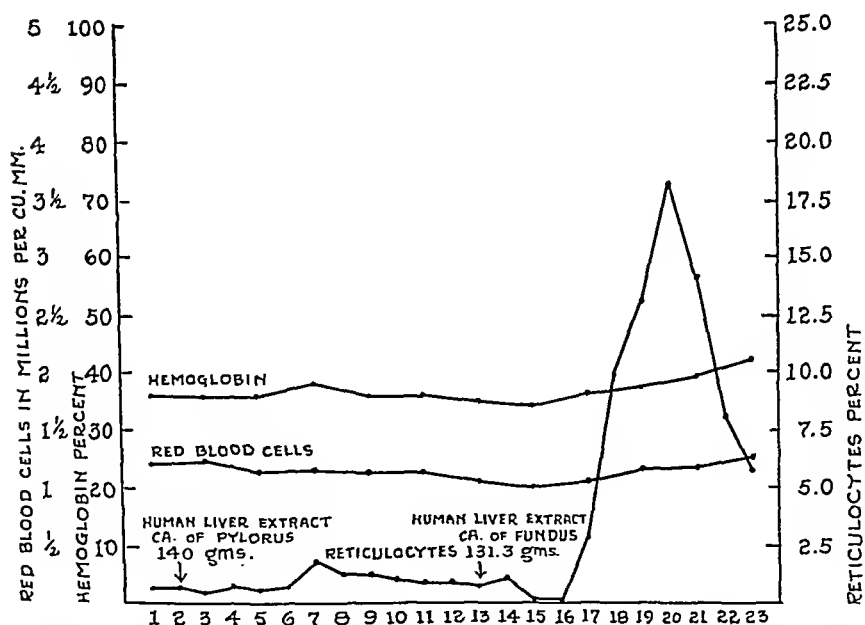


CHART 3.—Failure of response to human liver extract from a case of carcinoma of the pylorus, and response to liver extract from gastric carcinoma not involving the pylorus.

The slight elevation of reticulocytes which occurred on the fifth day following injection of the liver extract was traced to the accidental inclusion of liver in the diet. (This is an explanatory addendum to Fig. 3.)

EXPERIMENT 4.—*Extract from the liver of a patient with carcinoma of the cecum* (A-38-1165). The patient was a markedly emaciated colored female of 67, who complained of abdominal pain, vomiting, and loss of weight over a period of 3 months. Hematologic examination revealed 1,900,000 red cells per c.mm. The necropsy, which was performed 1 hour after death, revealed an adenocarcinoma of the cecum. The gastric mucosa was slightly atrophic but was otherwise normal.

The patient used for the determination of the antianemic principle in the liver was a white male of 74 with a typical Addisonian pernicious anemia. Hematologic examination revealed 1,500,000 red cells and 6000 white cells per c.mm. The hemoglobin value (Hellige) was 7.2 gm. (49%). The mean corpuscular volume was 127 cu. microns and the mean corpuscular hemoglobin 49 micromicrograms. The average percentage of reticulocytes was 0.8. No free hydrochloric acid was present in the gastric secretion either before or after the administration of histamine. Bone marrow puncture revealed numerous megaloblasts.

The intramuscular injection in a single dose of 16.5 cc. of liver extract (representing 150.2 gm. of whole liver) produced a reticulocyte response which reached a peak of 18.8% on the seventh day following. On the tenth day, when the reticulocyte count was 2.8%, the administration of 30 units of commercial liver extract (Lilly) caused another rise, which reached a peak of 16% on the eighth day following (Chart 4).

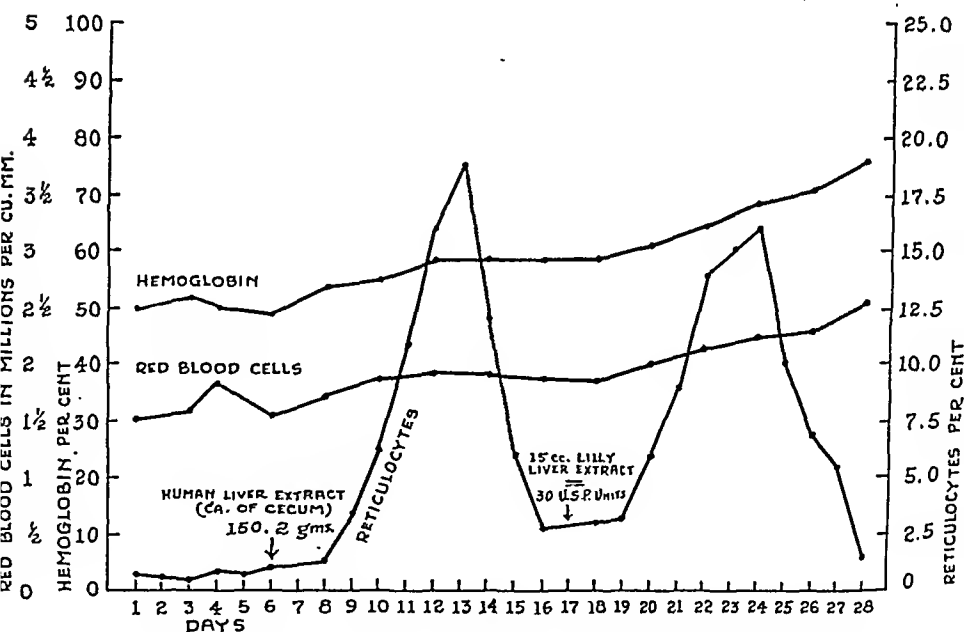


CHART 4.—The response to human liver extract from a case of carcinoma of the cecum.

**Summary.** An extract prepared from the liver of a patient whose death was due to scirrhus carcinoma of the pars pylorica failed to produce a reticulocyte response when administered to a patient with typical Addisonian pernicious anemia in relapse. A control extract prepared from the liver of a patient whose death was due to cerebral hemorrhage caused a stimulation of erythropoiesis in the same subject.

An extract prepared from the liver of a patient whose death was due to gastric carcinoma which involved the whole stomach except for a portion of the pars pylorica stimulated erythropoiesis in a patient with a macrocytic hyperchromic anemia.

The administration of the extracts prepared from the livers of the 2 patients with carcinoma of the stomach to another patient with typical Addisonian pernicious anemia in relapse confirmed the observations just described.

The hematopoietic potency was present in an extract prepared from the liver of a markedly emaciated patient whose death was due to carcinoma of the cecum, as demonstrated by its administration to a patient with typical Addisonian pernicious anemia.

The most active antianemic effect of the gastric mucosa, according to experimental observations, is obtained from the mucosa of the pyloric antrum. It seems significant, therefore, that in the cases herewith reported the antianemic principle was demonstrated to be absent in the liver of the patient whose pyloric mucosa was replaced by neoplastic tissue but to be present in the liver of the patient whose entire stomach, except for the pylorus, was involved by carcinoma.

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### FOLLICULAR LYMPHOBLASTOMA (GIANT LYMPH FOLLICLE HYPERPLASIA OF LYMPH NODES AND SPLEEN).

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THE clinical and pathologic entity variously termed "giant lymph follicle hyperplasia of lymph nodes and spleen," "giant follicular lymphadenopathy" or "follicular lymphoblastoma" was probably first described by Becker<sup>4</sup> in 1901. Descriptions of the condition also were made by Foix and Roemmele<sup>8</sup> in 1912, by Kettle<sup>13</sup> in 1920 and by de Jong<sup>12</sup> in 1921. In this country the disease was not generally recognized by the medical profession until Brill, Baehr



and Rosenthal<sup>5</sup> reported 2 cases in 1925. In this first American report the investigators stated that the hyperplastic process was apparently benign. In 1927 Symmers<sup>16a</sup> reported 3 cases and also stressed the relative benignity of the disease. In the same year, however, Baehr and Rosenthal,<sup>2</sup> in another report, revised their conception as to the benignity of the condition and called it "malignant lymph follicle hyperplasia."

Again, in 1931, Baehr and Rosenthal in collaboration with Klempner discussed the condition and stated that the disease is a form of lymphosarcoma which deserves to be distinguished from other varieties and proposed the term "follicular lymphoblastoma" to designate the condition. The chief characteristics of this disease were outlined as follows: 1, lymphadenopathy due to hyperplasia of the germinal centers of the lymph follicles; 2, splenomegaly due chiefly to enormous enlargement of Malpighian bodies; 3, absence of abnormal cells in the blood; 4, absence of anemia and cachexia; 5, tendency toward development of serous effusions in pleural and peritoneal cavities; 6, absence of involvement of tonsils and lymphatic apparatus of the gastro-intestinal tract; 7, tendency to lymphatic infiltration in the lacrimal gland, resulting in unilateral exophthalmos, and 8, multicentric origin throughout the body in the lymph follicles, whereas lymphosarcoma arises monocentrically and spreads by lymphatic extension.

In addition to the aforementioned contributions, Ikeda,<sup>10</sup> Terplan,<sup>17</sup> Ross,<sup>15</sup> McNee,<sup>14</sup> Cabot<sup>6</sup> and Ewing and Fein<sup>7</sup> have reported cases. Symmers<sup>16b</sup> recently has reviewed 25 new cases of giant lymph follicle hyperplasia. The termination of the disease in some of these cases was interesting. In one of them, necropsy revealed necrotic folliculitis of the lymph nodes. In 7 cases, polymorphous-cell sarcoma had developed. In 7 others, the condition was associated with Hodgkin's disease and in 4, with lymphatic leukemia.

The present report is based on a review of cases reported in the literature, together with a clinical and pathologic study of 13 cases in which the patients were seen at The Mayo Clinic. Of the latter, 7 of the patients have died. In 3 cases, necropsy was performed; in 8, the lymph nodes, and in 2, both lymph nodes and spleen, were available for histologic examination. Only 1 illustrative case will be reported, since the most important data from all of them have been arranged in Table 1.

**Illustrative Case.**—A white farmer, aged 42, registered at the clinic on May 9, 1935. He complained of shortness of breath and weakness of 8 months' duration. On further questioning it was learned that he had suffered from dysentery for years following his service in the United States Army. In 1923, he had noticed nodules as large as peanuts in his groin. In 1927, a mass about the size of a hen's egg had appeared in the right axilla and another developed in the left side of the neck; it was about as large as a walnut. All these signs gradually had disappeared until January, 1932, when the patient consulted his local physician because of generalized

TABLE 1.—CLINICAL DATA OF 13 PATIENTS WHO HAD FOLLICULAR LYMPHOBLASTOMA.

Case.	Age at onset and sex.*	Chief symptoms, signs and progress of disease.	Histologic diagnosis.	Reaction to radiotherapy.	Result.	Life duration, yrs.†
1	31M	Ing. lymphadenopathy . 1923 Ax. and cerv. lymphadenopathy . . . . 1927 Splenomegaly . . . . 1932 Hepatomegaly, loss of appetite, 1 yr. . . . 1934 Root pains . . . . 1935	Infl. lymph node (elsewhere) . 1932 Infl. lymph nodes (elsewhere) . 1935 F.L. of lymph nodes . . . . 1935 Ly.sa. of lymph nodes . . . . 1936	Excellent	Gen. involvement. G.I. hemorrhage Death 1937; Ly.sa.	14
2	60M	Asymptomatic except for discomfort of ing. hernia	F.L. (neeropsy). Lymph nodes and spleen, G.I. tract also involved	None given	Died 18 days after hernioplasty, of pul. embolism	?
3	44F	Progressive weakness . 1935 Pain in L. U. quadrant, 15 lbs. wt. loss, dyspnea, palpitation, gen. lymphadenopathy, splenomegaly, hepatomegaly, anemia, bilat. hydrothorax . . . . 1936	F.L. cerv. lymph nodes . . . . 1936 Neeropsy . . . . 1937	Leukopenia developed	Gen. involvement. Death 1937	1½
4	49M	Wt. loss and weakness . 1917 Cerv. lymphadenopathy, anemia, splenomegaly 1918	F.L. (cerv. lymph node) . . . . 1918 Also necropsy . 1922	None given	Gen. involvement. Chylothorax. Death 1922	5
5	42M	Weakness . . . . 1930 Splenomegaly, ing. lymphadenopathy . 1931 Tonsillitis . . . . 1933 Pains, back and legs . 1934 Gen. lymphadenopathy, exophthalmos . . . 1937 Nausea, vom., back pain 1938	F.L. of spleen . 1931 Tonsils . . . . 1933 Lymph nodes . 1936 Ly.sa. . . . 1937	Excellent	Gen. involvement. G.I. hemorrhage. Death 1938	7
6	56F	Abdominal mass . . 1931 (retroperitoneal nodes) Nausea, vom., diarrhea . 1936	F.L. mesenteric lymph node . 1931	Excellent	Gen. involvement Anemia. Death 1938	7
7	48M	Bilat. cerv. nodes . . 1929 A dominal distention . 1931 Dull pain, numbness . 1931 Numbness, tingling of feet . . . . 1931 Weakness, wt. loss and upper abd. pain . . 1931	F.L. cerv. lymph node . . . . 1932	No improvement	Death September 1932	3½
8	36M	Weakness, epigastric distress . . . . 1932 Fever . . . . 1933 Lymphadenopathy, splenomegaly, hepatomegaly, anemini . . 1933 Tonsillitis . . . . 1933	F.L. of spleen and lymph nodes and tonsils . . 1933	Excellent	Gen. involvement	7
9	47F	Cerv. and ax. lymphadenopathy . . . . 1935 Gen. lymphadenopathy 1936	F.L. cerv. lymph node . . . . 1936	Excellent	Asymptomatic 1939. Few small post. cerv. nodes on left side	4

\* Mean age nt onset was 47.7 years.

† Mean duration of life after onset for 6 patients who died of the disease was 6.3 years.

F.L. = Follicular lymphoblastoma. Ly.sa. = Lymphosarcoma.

TABLE 1.—CLINICAL DATA OF 13 PATIENTS WHO HAD FOLLICULAR LYMPHOBLASTOMA.  
(Continued.)

Case.	Age at onset and sex.*	Chief symptoms, signs and progress of disease.	Histologic diagnosis.	Reaction to radiotherapy.	Result.	Life duration, yrs.†
10	60M	Cerv. lymphadenopathy 1936	F.L. of submax. lymph node .	None given	Asymptomatic(?)	3
11	49M	Cerv. lymphadenopathy 1930 "Oce. bilious attacks" Epigastric mass . . . 1931 Pleural effusion . . . 1931	F.L. cerv. lymph node . . . 1931	Excellent	Asymptomatic 1939	8½
12	42F	Cerv. lymphadenopathy 1932	F.L. cerv. lymph node . . . 1932	Excellent	Heavy feeling in lower abd., otherwise asymptomatic 1939	7
13	54M	Gen. lymphadenopathy Aug. 1939	F.L. cerv. lymph node . . . 1939	Excellent	To return for checkup	1

\* Mean age at onset was 47.7 years.

† Mean duration of life after onset for 6 patients who died of the disease was 6.3 years.

F.L. = Follicular lymphoblastoma. Ly.sa. = Lymphosarcoma.

lymphadenopathy. The physician's report stated that the nodes were freely movable, were not tender or confluent, and were not attached to the skin or underlying tissue. The spleen was enlarged and was palpable 3 to 4 fingerbreadths below the costal margin. Results of hematologic examination were negative. A node was removed by the local physician and was reported by a pathologist to be inflammatory. Shortly before the patient came to the clinic another node had been removed elsewhere and histologic examination disclosed chronic lymphadenitis.

On physical examination the patient was found to be pale with hemorrhagic spots over the chest. The cervical, submental, epitrochlear and inguinal lymph nodes were enlarged. The spleen was enlarged and extended 2 inches below the level of the umbilicus. The liver also was moderately enlarged.

A lymph node, removed from the left supraclavicular region on June 4, 1935, showed a striking increase in the number and size of the follicles, with corresponding compression of the interfollicular tissue (Fig. 1, *a* and *b*). The cells of the follicles contained large pale-staining nuclei and few mitotic figures (Fig. 1, *c*). There were zones containing smaller lymphocytes about the follicles. There was slight proliferation of capillaries in the interfollicular zone. The capsule was not invaded. Because of the long history of this patient and the physical observations and since the histologic picture was that of giant lymph follicle hyperplasia, a diagnosis of follicular lymphoblastoma was made.

Röntgen therapy was administered for the lymphadenopathy and splenomegaly and the patient was dismissed on June 14, 1935. He improved and was well for several months, but returned at numerous times the following year because of pain in various situations. Röntgen therapy gave him much relief.

On Sept. 25, 1936, a lymph node removed from the left epitrochlear region showed hardly any traces of the architecture characteristic of giant lymph follicle hyperplasia. Most of the follicles had fused with one another

and had resulted in complete destruction of the architecture (Fig. 1, *d*). There was invasion of the capsule and surrounding tissue.

The patient's last admission to the clinic was on Dec. 22, 1937, when he was suffering from gastro-intestinal hemorrhage. Transfusions of blood were necessary. A letter from his local physician stated that the patient died on Dec. 27, 1937, the cause of death apparently being massive gastro-intestinal hemorrhage. Necropsy was not performed.

**COMMENT.** This case illustrates the relatively benign course that the disease in question may take. Lymphadenopathy had extended over a period of 14 years and was marked by remissions and exacerbations. Similar cases have been noted by other workers and originally led Baehr, Brill and Rosenthal to believe that the condition was benign, although they later changed their opinion. The present case also emphasizes the difficulties that may confront the pathologist in making a diagnosis. The histologic appearance of tissue first removed elsewhere, and also the tissue later removed at biopsy at the clinic, was that of giant lymph follicle hyperplasia. A somewhat similar appearance is often seen, however, as a reaction of lymph nodes to toxic or inflammatory conditions and it can be understood how easy it would be to err in the histologic diagnosis if the histologist were unfamiliar with the disease.

**Clinical Features.** Fifty-nine cases were collected from the literature and analyzed together with the 13 cases referred to herein, making a total of 72 cases. The mean age of all these patients was 39.3 years. The oldest patient was 77, the youngest 2 years. Only 9 patients, however, were less than 30 years of age. There were 47 males and 25 females.

The disease under consideration generally begins insidiously. Often, the first symptom is enlargement of local lymph nodes unaccompanied by any feeling of ill-health on the part of the patient. This has been emphasized by many investigators. The disease produced no symptoms for 1 of our patients (Case 2) and was unsuspected until it was disclosed at necropsy (Table 1). Absence of anemia or cachexia may mislead the physician into suspecting an inflammatory or toxic agent as the cause of the lymphadenopathy. An interesting observation in our present series was the fact that 4 patients complained of weakness as one of the symptoms first noticed. This weakness was accompanied by loss of weight in only 1 instance.

Of all cases reported, including the present series, the regional lymph nodes were first enlarged in 33, whereas in 32 cases there was more or less generalized involvement of lymph nodes at the onset of the disease.

The nodes vary in diameter from 1 to 5 cm. or more. In the early stages of the condition, at least, they are discrete, movable and painless. Later they are very closely packed and appear to be confluent. As shown by our Case 1 and other cases reported by

Symmers, the nodes may diminish spontaneously in size or disappear for a time.

The cervical nodes are generally the first to be involved, although the disease may appear earlier in the axillary or inguinal group of nodes and in one of our cases the mesenteric nodes were apparently the first to be affected. An interesting observation in the present series in this connection is the frequency with which the patients complained of gastro-intestinal symptoms. Seven patients had such complaints as a sensation of fullness, belching, gas, loss of appetite, constipation and diarrhea. These symptoms, in 3 patients, were probably related to the presence of an enlarged spleen. The possibility that these symptoms were due, in some cases, to involvement of the mesenteric and retroperitoneal lymph nodes with subsequent disturbances in lymphatic absorption and drainage also must be considered. These nodes were found to be involved in the patients who had these symptoms.

Splenic enlargement also is a frequent occurrence. It was present in 44 cases out of the 72 cases (including our 13 cases) reported in the literature (61.1%). In some cases reported in the literature it was the first symptom and was unaccompanied by appreciable lymphadenopathy. Of the cases in which patients came to necropsy, the spleen was enlarged in all. Hepatic enlargement does not occur so frequently as splenic and was described in only 8 cases.

The tendency toward development of serous effusion in pleural and peritoneal cavities has been mentioned as a characteristic feature of this disease. Ascites was present in 5 and hydrothorax in 9 cases reported in the literature. Exophthalmos as a result of infiltration of the lacrimal gland has been described by Baehr<sup>1</sup> as occurring in 4 of the 19 cases which he discussed. It afflicted only 1 patient in our series (Case 5) and has not been described by other workers (Table 1).

Baehr, Rosenthal and Klemperer<sup>3</sup> emphasized the absence of involvement of tonsils and the lymphatic apparatus of the gastro-intestinal tract. Tonsillar enlargement and tonsillectomy are recorded concerning some of the cases in the literature but no descriptions have been provided of the histologic appearances of removed tissue. In our own series there were 2 cases (Cases 5 and 8) in which involvement of the tonsils occurred, and 1 case (Case 2) in which the lymphatic tissue of the gastro-intestinal tract was found to be involved at necropsy (Fig. 2, a).

**Hematologic Observations.** Anemia is not often encountered at the onset of the disease being described. It was mentioned in only 6 cases reported in the literature and found in only 3 of our cases (Cases 3, 4 and 8). It is of the hypochromic variety and is not as a rule severe. The leukocyte count is generally normal but slight leukopenia may be present. Studies of the blood smears revealed no significant abnormalities among our patients. Symmers, how-

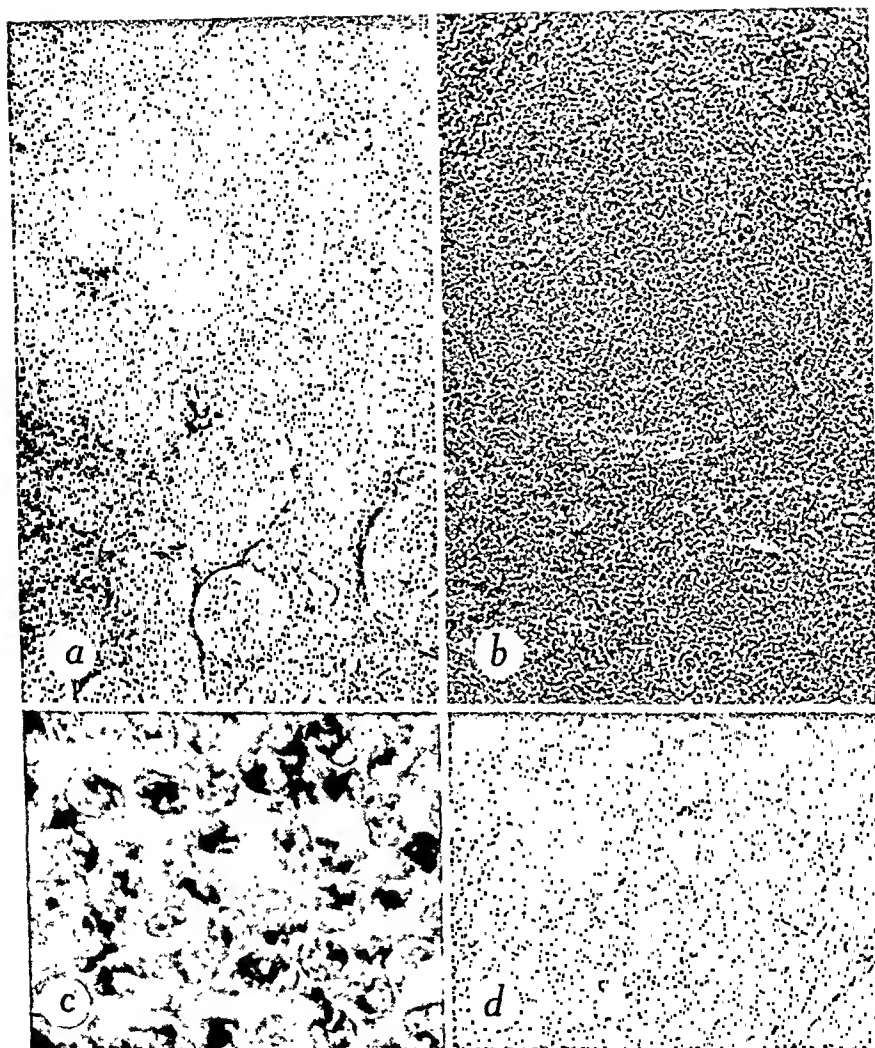


FIG. 1.—Histologic sections of lymph nodes from Case 1; *a*, left supraclavicular node removed June 4, 1935, with large hyperplastic follicles (hematoxylin and eosin  $\times 100$ ); *b*, same section shown in Figure 1*a* ( $\times 100$ ); *c*, structure of the nuclei in a follicle ( $\times 1000$ ); *d*, left epitrochlear lymph node, removed September 25, 1936; lymphosarcoma (hematoxylin and eosin  $\times 25$ ).

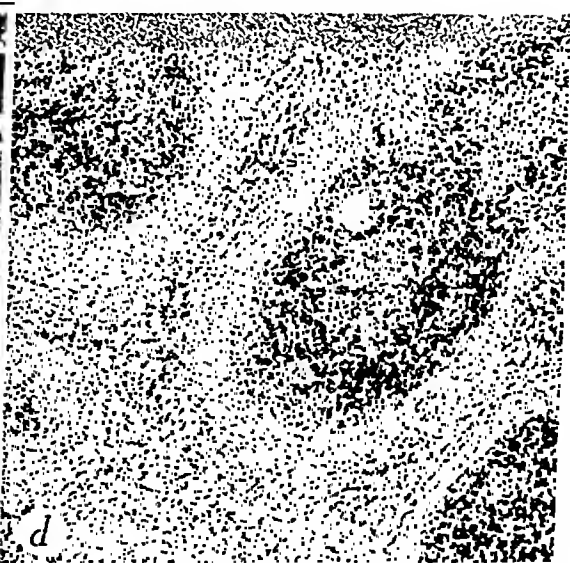
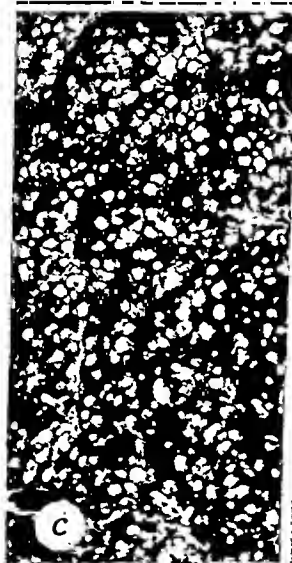
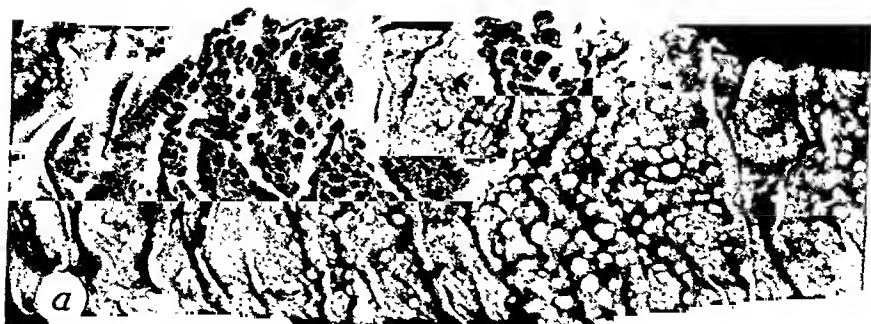


FIG. 2.—Follicular lymphoblastoma; *a*, segment of ileum (Case 2); *b*, cut surface of spleen (Case 3) compared with a normal spleen; *c*, close-up photograph of spleen (Case 3); *d*, photomicrograph of spleen (Case 3) (hematoxylin and eosin  $\times 32$ ).

ever, has reported 3 cases of the disease in which lymphatic leukemia developed and 1 in which the disease apparently was associated with lymphatic leukemia.

**Duration.** Data concerning the duration of the disease were available in 53 cases, including 11 reported at this time. The average duration of life after appearance of the disease in 24 patients who were living at the time they were reported on was 4.6 years. Two of the patients had been living 17 years. The average duration for 29 of those who had died was 4.8 years. All workers agreed that this disease offers a better prognosis than do other varieties of lymphosarcoma. According to Baehr the average duration for patients who have other types of lymphosarcoma, excluding involvement of the gastro-intestinal tract, was 11 months. According to Jackson,<sup>11</sup> the average duration for a patient who had Hodgkin's disease was 2.5 years, whereas that for one who had giant follicle lymphoma (follicular lymphoblastoma) was 4 years.

**Reaction to Radiotherapy.**—Workers generally agreed that follicular lymphoblastoma responds more readily to Roentgen therapy than does any other neoplastic disease of the lymph nodes. The enlarged nodes and spleen often have been described as "melting away" after the first treatment. Of 44 patients reported on in the literature, including the present series, 38 responded well to radiotherapy, whereas only 6 responded poorly. Unfortunately, after repeated treatments the disease no longer responds so readily as at first and finally the Roentgen rays fail to affect the progress of the disease at all. No permanent cures have as yet been reported.

**Gross Pathologic Anatomy.** Although almost any organ may become involved in the pathologic process of the disease in question, the lymph nodes and spleen are generally the first structures to be involved or to reveal the most marked and typical changes. Characteristic lesions have been described less frequently as occurring in the liver and bone marrow.

Usually, the lymph nodes are firm in consistency and in the cut section the enlarged follicles can be seen by the naked eye. The capsule generally is not invaded early in the disease.

The spleen usually is greatly enlarged. The average weight of the spleens in 19 cases reported in the literature, including the present series, was 1665 gm. The largest, that described by de Jong, weighed 6500 gm.; the largest spleen in our series weighed 2300 gm. The spleen is firm and may be covered by a hyaline substance. Adhesions are frequently present. The purplish-red cut surface of the organ is studded with numerous, pale, grayish, somewhat raised portions varying from 1 to 3 mm. in diameter (Fig. 2, *b* and *c*). Many of these raised structures are greatly hypertrophied Malpighian corpuscles (Fig. 2, *d*).

**Histopathology.** Histologic examination of lymph nodes removed in the early stage of the disease reveals a striking increase in the



size and number of the follicles (Fig. 1, *a*). The follicles vary in size but nearly all are larger than normal. Variation in shape may or may not be marked. They are mostly round but may be ovoid, hook or clover-leaf-shaped. The central portions generally consist of larger cells with large faintly-staining nuclei and numerous mitotic figures. These cells are generally regarded as lymphoblasts but in some instances they appear to arise from reticulum cells. About the periphery of the follicles small deeply-staining lymphocytes are densely packed and may appear to be arranged in circumferential rows. Occasionally, the enlarged follicles consist entirely of small or medium-sized lymphocytes which are closely packed. By the use of silver impregnation methods only relatively few reticulum fibrils can be demonstrated in the follicles.

Because of the tremendous increase in size and number of the follicles, the interfollicular zones are generally narrowed and compressed. The predominating cell in the interfollicular tissue is the lymphocyte, but there often is increased proliferation of capillaries and endothelial cells. The increase in the number of capillaries may be more apparent than real because of the compression of the interfollicular zones by the rapidly growing follicles. The endothelial proliferation, however, is definite. These cells often fill the lumens of the capillaries and in some instances migrate away from the vessel and lose their attachment to it. The lymphatic sinuses are always narrowed and may be obliterated. By silver impregnation methods an apparent increase in the number and size of the reticulum fibers can be demonstrated.

In some cases, the involved lymph nodes maintain the same histologic appearance throughout the disease. In 2 of our cases, later biopsies revealed the histologic picture of lymphosarcoma. Traces of the follicular structure still could be found in these lymph nodes, however.

In sections of the involved spleen there is a striking numerical and dimensional increase in the Malpighian bodies as well as numerous independent nodular proliferations of lymphocytes which may or may not be connected with Malpighian bodies (Fig. 2, *d*). The increase in the size of these structures can be attributed, in some cases, to the proliferation of small, deeply-staining lymphocytes and in other cases to the proliferation of larger cells with large, pale-staining nuclei. Both types of cells are found, however, in all Malpighian bodies and nodules in varying numbers. Mitotic figures are not infrequent. As a result of the increase in size and number of these structures, compression of the interfollicular splenic pulp and sinuses is common. Occasionally, there is an apparent proliferation of capillaries, in both follicles and pulp. The littoral (reticulum) cells lining the sinuses also, occasionally, appear to be increased.

Unfortunately, the histologic appearance of follicular lympho-

blastoma in its early stages is sometimes mistaken for "inflammatory" hyperplasia of the secondary nodules of lymph nodes. The similarity is, however, only a superficial one and a distinction between the two conditions is generally not difficult to make if the histopathologist is familiar with follicular lymphoblastoma and its histologic characteristics.

To establish histologic criteria which would enable the histopathologist to differentiate inflammatory hyperplasia of the secondary centers from follicular lymphoblastoma, a study was made of biopsied specimens of lymph nodes from 50 cases in which a diagnosis of inflammatory lymphadenopathy had been made. In each case the diagnosis had been confirmed by the subsequent clinical course of the patient. In none of these cases was there any difficulty in distinguishing the histologic appearance of the nodes from that of follicular lymphoblastoma. The points which were found to be of value in differentiating the two conditions have been listed in Table 2.

TABLE 2.—HISTOLOGIC DIFFERENCES BETWEEN FOLLICULAR LYMPHOBLASTOMA AND INFLAMMATORY HYPERPLASIA.

	Follicular lymphoblastoma.	Simple hyperplasia of inflammatory or toxic origin.
Follicles	Larger and more numerous	Smaller and less numerous
	Closely packed	Scattered
	Diffuse throughout node	Arranged around cortex in concentric rows
	Frequent in medulla	Few in medulla
	Uniformly large	Vary in size
	Tend to fuse	Are discrete
Interfollicular tissue	Cells densely packed	Cells scattered
	Condensation of reticulum	Loose reticulum
	Sinuses narrowed or blocked	Sinuses open—often dilated
	Slight proliferation of reticular cells	Marked proliferation of reticular cells

The most helpful histologic sign in distinguishing follicular lymphoblastoma from inflammatory hyperplasia was the greater numerical and dimensional increase in the follicles in the presence of the former condition. In addition to this quantitative difference, the tendency of the follicles to fuse with each other and the narrowing and obliteration of the lymphatic sinuses were found to be typical of follicular lymphoblastoma and were very helpful as diagnostic signs. The presence of mitotic figures was of little help. Such figures are as frequently present in one condition as in the other. In occasional cases, in which a conclusion could not be reached, even after careful study, it was found convenient to reserve the diagnosis and to use a non-committal term such as "follicular hypertrophy" to describe the histologic appearance. Further observation and subsequent biopsy generally substantiated the suspicion that we were concerned with an early instance of follicular lymphoblastoma.

**Classification of Follicular Lymphoblastoma.** Baehr, Klemperer and Rosenthal stated in 1931 that follicular lymphoblastoma is a form of lymphosarcoma which deserves to be distinguished as a pathologic entity and that it may form a connecting link between systemic hyperplasia of the lymphatic tissue (aleukemic lymphadenosis) and lymphosarcomatosis. Symmers in 1938 reported 3 cases of giant follicular lymphadenopathy in which the condition terminated as lymphatic leukemia, and this would seem to support the conception of Baehr, Klemperer and Rosenthal. Ghon and Roman<sup>9</sup> in 1916 described the tendency toward formation of new follicles in 10 cases of lymphosarcoma but the condition in these cases did not manifest itself as does follicular lymphoblastoma, either clinically or anatomically. As has been pointed out by Baehr and associates, follicular lymphoblastoma has a multicentric origin in the lymph follicles, throughout the body, whereas lymphosarcoma arises monocentrically and spreads by lymphatic or hematogenous extension. Ross thought the condition to be hyperplasia affecting undifferentiated cells with unrestricted potency for differentiation, and has classified it as "lymphoid reticulosis." This point of view assumes that the reticular cells are chiefly involved in the proliferative process, whereas most workers believe that homoplastic proliferation of lymphocytes is the more important process. Symmers stated that giant follicular lymphadenopathy is probably of inflammatory or toxic origin. This conception receives some support from the relatively benign early course of the disease, but it does not explain the fatal termination of the condition among patients who have been followed over a long period of time.

The conception of Baehr and associates of the position of follicular lymphoblastoma as a connecting link between systemic hyperplasia of the lymphatic system and lymphosarcomatosis has much to recommend it. It must be pointed out, however, that follicular lymphoblastoma is more amenable to Roentgen therapy and generally runs a much longer course than either aleukemic lymphadenosis or lymphosarcomatosis.

**Summary and Conclusions.** A clinical and pathologic entity variously called "giant follicle hyperplasia of lymph nodes and spleen," "giant follicular lymphadenopathy" and "follicular lymphoblastoma" has been described in the literature in recent years with increasing frequency. The condition is characterized by an insidious onset with regional or general lymphadenopathy, splenomegaly, the absence of anemia or abnormal cells in the blood and by the great radiosensitivity of the lesions. The average duration of life after the appearance of the disease is 4.5 years, but 2 patients have lived as long as 17 years with this disease.

The characteristic histologic changes occurring early in the disease consist of an increase in the number and size of the follicles of the lymph nodes and of the Malpighian corpuscles of the spleen.

There is a tendency toward fusion of the follicles and the lymphatic sinuses are generally narrowed or obliterated.

There is a superficial resemblance between the histologic appearance of follicular lymphoblastoma and the histologic appearance of hypertrophy of the secondary centers of lymph nodes resulting from toxic or inflammatory conditions. The histologic criteria which enable the histopathologist to distinguish the two conditions have been outlined.

In certain rare instances in which the histologic appearance is not typical of either follicular lymphoblastoma or inflammation, it may be wise to reserve diagnosis and merely to use a descriptive, non-committal term, such as "follicular hypertrophy," to denote the condition. Subsequent observation and biopsy frequently will bear out the suspicion that the condition in question is an early instance of follicular lymphoblastoma.

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## THROMBOSIS OF THE AXILLARY AND SUBCLAVIAN VEINS.

### WITH A NOTE ON THE POST-THROMBOTIC SYNDROME.

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THROMBOSIS of the axillary and subclavian veins is an uncommon condition. From a review of the literature of the last 50 years, we were able to collect less than 150 cases. However, the number of reports have been steadily increasing, and undoubtedly it is more frequent than a study of the records leads one to believe. The fact that only 23 articles have dealt with more than one case shows that the experience of a single author has been limited. The bases for this report are the observations on 17 cases of thrombosis of the axillary and subclavian veins. In addition to the usual clinical data, the

venous pressures of the normal and affected extremity have been recorded, and venographs demonstrating the point of obstruction and outlining the collateral circulation have been made in most of the cases. From these studies certain facts have been learned concerning the basic pathology, the altered physiology during the early and late stages, the development of collateral venous circulation, and finally the end results of this condition.

Acute thrombosis of the axillary and subclavian veins produces a typical symptom complex, regardless of the etiology of the thrombosis. The cardinal symptoms are pain in the arm and shoulder; massive pitting edema of the entire extremity; weakness and partial loss of function of the arm; preservation of the radial pulse; elevation of systolic pressure on the affected side; palpable, tender, cord-like swelling along the course of the brachial, basilic and axillary veins; marked elevation of the local venous pressure; and a decrease in the oxygen content of venous blood of the affected arm.

The essential pathology of thrombosis of the axillary and subclavian veins is that of obstruction of the return blood flow from the hand and arm, vasospasm, an increase in local venous pressure, and an escape of fluid into the tissue. Many writers have used the term "primary thrombosis of the axillary vein," but, as a matter of fact, the thrombosis is seldom confined to the axillary vein alone. In almost all instances it involves the entire axillary, portions of the subclavian, the basilic and brachial veins, occasionally the external jugular, and rarely the internal jugular vein. The entire thrombus may be absorbed, or it may become organized and permanently obstruct the vessels. There may be a recanalization of the lumen, but this is usually incomplete, and the return circulation must be carried on by the newly developed collaterals.

There are several forms of thrombosis of the axillary and subclavian veins. Although some of the etiologic factors have not been definitely established in these several forms, the following classifications seem complete enough for practical purposes. 1. PRIMARY THROMBOSIS: (a) Thrombophlebitis (Bacterial); (b) Phlebothrombosis (Non-bacterial, traumatic or effort thrombosis). 2. SECONDARY THROMBOSIS: (a) Thrombophlebitis from regional infection; (b) Thrombosis from malignancies of the axilla and chest. 3. POST-THROMBOTIC SYNDROME.

The 17 cases which we have had the opportunity to study at the Charity Hospital, New Orleans, and at Gallinger Municipal Hospital, Washington, D. C., provide examples for each of the types in the above classification. Four were classified as primary and one as secondary thrombophlebitis. Four were classified as primary phlebothrombosis. Eight of the cases fell in the group of secondary thrombosis from malignancies of the chest and axilla.

**Thrombophlebitis.** True thrombophlebitis of the axillary and subclavian veins is indeed a rare condition when compared with the

frequency of this disease in the vessels of the lower extremities. Thrombophlebitis presents definite constitutional and local signs of inflammation. The body temperature is elevated, the pulse is accelerated, and there is a leukocytosis. The skin over the involved veins is warm, reddened, tender to touch, and painful on manipulation. Pitting edema of the hand and entire arm develops rapidly. It occurs most often in cardiac patients in whom there is a slowing of the venous blood flow (Fig. 1). The phlebitis may be secondary to an infection in the region of these veins or their tributaries. Blumer<sup>3</sup> reported a case secondary to pulmonary tuberculosis. Jakobson<sup>8</sup> reported a case following influenza. McGoogan and Simmons<sup>11</sup> described a case of thrombophlebitis beginning in the left side of the neck and extending into the subclavian and axillary veins in a patient during the puerperium.

**Case Reports.** CASE 1.—In one of our own cases the thrombophlebitis was secondary to a skin infection of the neck. A small furuncle developed over the external jugular vein, and the infection extended to the vein wall and produced a thrombosis. The thrombus then spread from the external jugular to the subclavian, axillary, basilic and brachial veins. This patient was a cardiac in a state of congestive failure. She presented the typical findings of acute thrombophlebitis of the veins of the upper arm, axilla and neck, with massive edema of the arm. There was a mild constitutional reaction; temperature, 101° F., and a leukocytosis of 14,000.

CASE 2.—Our second patient had had hypertension for many years. Shortly before onset of the axillary and subclavian vein thrombosis she had "chills and fever." The following day she awoke with acute swelling of the left arm. There was increased heat, redness and tenderness along the veins of the upper arm, axilla and neck. She had a febrile temperature and leukocytosis.

CASE 3.—The third case was also a hypertensive patient, and in addition was in a state of congestive failure. After being confined to bed for several days, she developed thrombophlebitis of the veins of the left side of the neck which gradually extended to the subclavian and axillary veins. She exhibited the cardinal symptoms of acute thrombophlebitis, including fever and leukocytosis.

CASES 4 and 5.—The fourth and fifth cases were quite similar in character, occurring in elderly white females several weeks after the onset of acute congestive cardiac failure.

Four of these recovered from the acute stage of the thrombophlebitis, but later showed some residual signs and symptoms. One died of congestive failure.

In thrombophlebitis of the axillary and subclavian veins, the signs of the acute infection usually subside within a few days. The edema gradually disappears as the collateral circulation develops (Fig. 2). While a few of the reported cases have died, the cause of death has been the associated disease and not the thrombosis. Embolism rarely follows.

There are probably two reasons why thrombophlebitis is so infrequent in the upper extremity. The most important is the rapid emptying of the venous system of the arm by almost continuous

use of the limb. The second factor, which to me seems important, is the length of the course through which the blood must flow. The distance of the circuit in the upper extremities is so short that stasis is unusual. For whatever reasons, it is an established fact that true thrombophlebitis of the axillary and subclavian veins is indeed a rare disease.



FIG. 1.—Edema of arm from acute thrombosis of axillary and subclavian veins in a cardiac patient.

**Primary Phlebothrombosis (Traumatic or Effort Thrombosis).** By phlebothrombosis is meant a sterile or non-bacterial form of thrombosis. This is by far the most common form of thrombosis of the axillary and subclavian veins. In this group we have included the so-called "effort type," as well as all cases resulting from direct and indirect trauma to the vein wall, the intima, the valves or adjacent tributaries. The symptoms of phlebothrombosis are identical with those of true thrombophlebitis, except that the local and constitutional signs of inflammation are absent. The onset is usually quite acute, but may be gradual. Pain is the first symptom. It begins as a "sticking" or "stinging" type, involving the entire arm and shoulder girdle. Swelling of the arm and hand develops rapidly, so that in the course of a few hours the entire extremity is enormously enlarged. There is an associated arterial spasm which may cause the

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LEGENDS FOR FIGS. 2 AND 3.

FIG. 2.—Venograph showing the developing venous collaterals in a case of thrombophlebitis of the axillary and subclavian veins; 10 days after onset.

FIG. 3.—Collateral venous circulation following permanent occlusion of the axillary and subclavian veins, from primary phlebothrombosis.

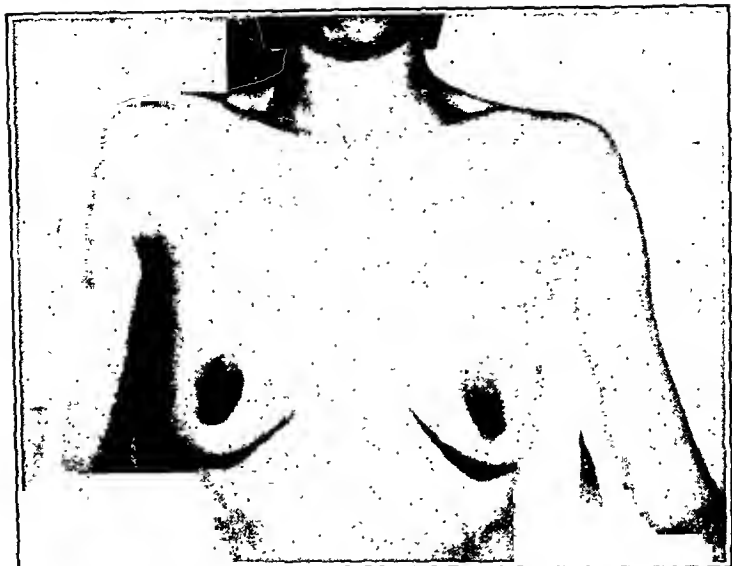


FIG. 2.



FIG. 3.





FIG. 4.—Massive edema of arm and hand from thrombosis of the axillary and subclavian veins in a case of recurrent carcinoma of the breast. The thrombosis followed invasion of the axillary by the tumor cells.

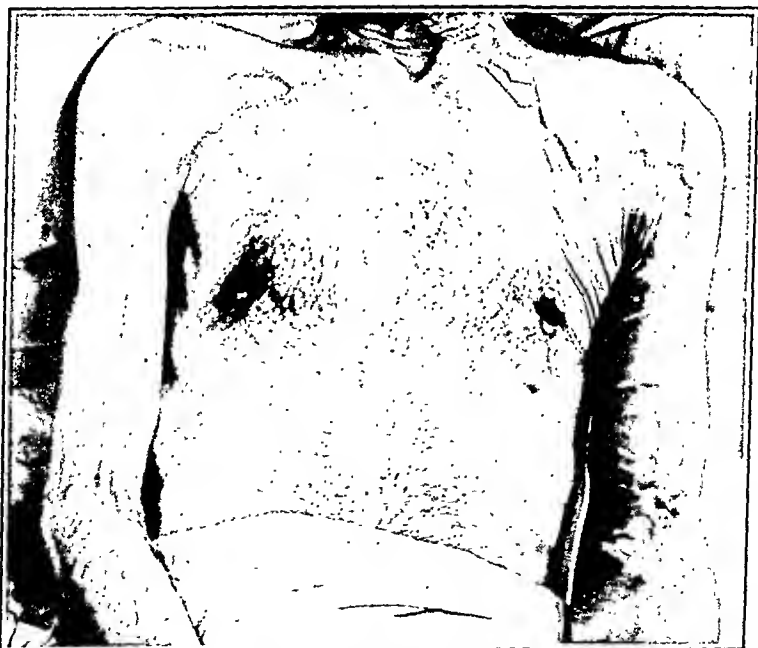


FIG. 5.—Venous collateral circulation over the arm and shoulder after occlusion of the subclavian vein by thrombosis secondary to metastatic carcinoma from lung.

hands to feel cold and numb and produce a slight cyanosis of the finger tips. The extremity is perfectly useless, and the patient supports it with his normal limb. The arterial pulse can be easily palpated. Along the inner surface of the upper arm a firm, tender, cordlike mass can be felt extending up through the axilla and to the chest wall. Usually this cord involves the basilic, the brachials, the axillary, and often the external jugular veins. The course of events is quite typical. The maximum swelling is usually reached within 24 hours after onset and persists from a few days to several weeks. As the edema subsides, there is evidence of superficial venous collaterals developing over the upper arm, shoulder and anterior part of the chest wall (Fig. 3). From this stage on the cases vary considerably and will be discussed later.

The explanation of the development of thrombosis following a direct crushing or contusing injury to the axillary vein is obvious. However, only a very few cases have resulted from such an accident. In reviewing the reported cases one is immediately struck with the great variety of circumstances under which the condition develops. It occurs usually in healthy individuals. The right arm is most frequently involved. There has been no uniformity as to the type of trauma, the mode of exercise or position of the arm at the time of injury. It has followed indirect trauma, such as a fall on the shoulder; and direct trauma, such as a contusion over the axillary region. It has followed the simple task of stirring pudding. It has resulted from such violent exercise as rowing a boat. In many, the thrombosis occurred during the patient's sleep and in whom there was no preceding history of trauma or any unusual strain.

CASES 6 to 9.—Four of our cases have been classified as phlebothrombosis. In one, the thrombosis occurred after sleeping with the arm extended upward under the head. In another, it followed a hard day's work at washing clothes. In the third case, there was no history as to preceding effort or strain, but there was no constitutional reaction, and the course was typical of phlebothrombosis. The fourth resulted from a severe contusing injury to the upper left arm and shoulder.

Several attempts have been made to explain the mechanism of the injury to the axillary or subclavian veins in the so-called "effort or primary thrombosis," which we prefer to call phlebothrombosis. Von Schrotter, 1884,<sup>13</sup> is credited with first describing this traumatic type of axillary vein thrombosis. He thought that an unusual muscle strain stretched the axillary vein and caused damage to its wall, and thrombosis resulted. He did not consider any peculiar anatomic features that might be at play. Cadenat<sup>4</sup> introduced another factor, that of distention of the vein by respiratory effort; and he thought that this produced an injury to the venous lining. Willan<sup>16</sup> believed that the axillary vein was stretched between the clavicle and the first rib, producing sufficient injury to cause a thrombosis. Lowenstein<sup>10</sup> concluded from his studies on cadavers that there was a two-

fold basis for the development of thrombosis. First, there was a venous stasis or circulation slowing produced by forced expiration that characterized effort. Second, marked abduction or extension of the arm, probably with lateral rotation, produced a pronounced pressure by the costocoracoid ligament on the axillary vein, with resulting changes in the vascular endothelium sufficient to produce thrombosis. Gould and Patey<sup>7</sup> expressed the opinion that the pressure of the subclavius muscle on the axillary vein caused a distention of the vein and then a rupture of the delicate subclavio-axillary valves.

In a previous communication<sup>15</sup> we reported the results of a series of anatomic studies on fresh cadavers which were made with the object of determining the influence of the position of the arm upon the axillary vein. We showed that when the arm was in the abducted position, the point of compression of the axillary vein was over the subscapularis muscle beneath the head of the humerus. By means of venographs we were able to confirm this on the living subject. We also found that there was an actual stretching of the axillary vein proximal to the point of compression. We were unable to produce constriction of the axillary vein at any other point. These findings seem important because they were demonstrated on cadavers before there were any postmortem contractions of the muscles or fixation of the tissues. Furthermore, they were actually observed in the living subject. We were able to confirm Cadenat's suggestion that respiratory effort might cause considerable distention of the axillary vein under certain circumstances. The arm was abducted in order to constrict and fix the axillary vein over the subscapularis muscle. Then axillary venous pressure determinations under forced respiration were recorded. There were wide fluctuations in the pressure, denoting alternate collapse and great distention of the axillary vein. It is conceivable that such sudden stretching of the vein might cause some injury which would lead to thrombosis. In many of the reports it has been shown that thrombosis followed severe exercise in which the respiratory efforts were strained.

A considerable number of cases have resulted from sleeping either with the arm elevated over the head or folded under the body. In these positions the axillary vein may be completely compressed and fixed. Then, due to periodic increase in expiratory effort, the vein may become distended. If it so happens that the blood flow has been retarded by the compression or constriction, damage may result from the overdistention. Another factor probably enters into these cases. When the venous blood flow is obstructed, there is a lowering of its oxygen content. This is a progressive condition: the more complete and the more lasting the obstruction, the greater the fall in the oxygen of the venous blood. This may reach a stage in which the lining cells of the involved vessels are so damaged that physical changes occur from anoxemia and provide a nidus for the

formation of a clot. Furthermore, it is possible that the intimal cells at the constricted area may be injured by the force of the compression.

Some writers have mentioned venospasm as a possible cause of thrombosis. Injury to a vessel, whether it is traumatic, inflammatory or thermal, may cause a spasm or contraction of that vessel. Vasospasm may result from sympathetic irritation. During the period of spasm the lumen of the vessel may be almost occluded and cause a marked retardation of blood flow. If the exciting cause of the venospasm has also damaged the vein wall or its intima, thrombosis might result. It seems that venospasm must be a secondary and not the primary factor in the production of axillary and subclavian vein thrombosis.

From a careful study of the literature and a consideration of our anatomic and clinical studies, it seems reasonable to state that there are no known anatomic peculiarities or blood diseases that predispose to thrombosis of the axillary and subclavian veins. It seems clear that two factors must always be at play in order for an intravascular thrombus to develop. There must be some damage to the vessel, then a slowing down of the blood flow. The injury may be to the valves, the intima, or the entire vein wall may be damaged. It may result from a direct crushing or contusing blow over the veins. It may result from overdistention of the axillary vein from violent respiratory effort, provided the vein is sufficiently compressed at one point so that the blood cannot empty into its tributaries. If the outlet to the tributaries is not obstructed, the results of forced respiratory efforts are expended by allowing a back flow of the venous blood into these vessels, and overdistention is prevented.

**Secondary Thrombosis from Malignancies of Chest and Axilla.** Secondary thrombosis of the axillary and subclavian veins from malignancies of the axilla and chest has not received sufficient emphasis.<sup>14a</sup> From a study of approximately 60 cases of post-operative edema of the arm (following radical mastectomy for carcinoma of the breast), we found that the cause of the edema was an obstruction of the venous return from the arm in about 90% of the cases. The obstruction in some was the result of scar formation; in others, direct involvement of the axillary or subclavian vein by the carcinoma.

**CASES 10 to 14.**—In 5 of our cases the cause of the venous obstruction was proved at autopsy to be due to thrombosis of the axillary and subclavian veins (Fig. 4). In some, the carcinoma cells were found to have penetrated the vein wall and invaded the lumen. Around these cells a clot had formed which completely occluded the vessel. In others, the new growth had involved only the wall, and yet the vessel was completely filled with a thrombus, which was firmly attached to the intima. In one, the thrombosis apparently resulted from compression of the veins by enlarged metastatic glands.

CASES 15 to 17.—In 3 other cases in this present series the axillary and subclavian thrombosis was secondary to primary lung carcinoma. The veins were involved in a similar manner to those following carcinoma of the breast (Fig. 5).

We have been particularly concerned in our studies with the development of the collateral venous circulation. By means of venographs we have actually visualized the venous circulation of the involved region in most of the cases. Venographic studies have been made as early as 48 hours after onset, and as late as 22 years following the development of the thrombosis. Therefore, all stages of the process of the formation of collateral circulation have been visualized. From these observations it has been possible to demonstrate the common routes through which the collaterals develop, the approximate rate, and the extent of the collateral formation.

Regardless of the type of thrombosis, the development of collateral circulation follows a more or less definite course, depending primarily upon the extent of the thrombosis (Fig. 6). When it does not extend beyond the axillary vein, the development of the collaterals is rapid. But when the thrombosis is more widespread, the collaterals develop more slowly. The important tributaries taking part in the development of the collaterals are the superficial veins over the anterior shoulder and chest, the veins following the acromiothoracic artery, the long thoracic, and the cephalic vein. Through this last-named vein the collaterals connect with the superficial and deep veins in the neck. The collaterals may cross the midline of the neck and communicate with the veins on the opposite side. The flow may be retrograde, flowing upward through the external jugular to enter the cerebral vessels. The superficial collaterals over the upper arm and anterior chest usually drain into the mammary, acromiothoracic, long thoracic, intercostals, or internal mammary. There are many small collaterals formed directly through the axilla which connect with the subclavian proximal to the occlusion.

In the cases of secondary thrombosis following radical amputation of the breast, there is less chance for the development of adequate collaterals. Due to the nature of the operation, the acromiothoracic, often the long thoracic, and sometimes the cephalic, has been sacrificed. Furthermore, attempts at collateral formation are frustrated because of the formation of scar tissue through which the new veins must grow.

**Post-thrombotic Syndrome.** Although the acute stages of phlebotrombosis and thrombophlebitis rapidly abate, the altered physiology of the circulation may not be corrected. There may remain sufficient obstruction to the venous return to produce more or less permanent symptoms. To this symptom complex we have applied the term "post-thrombotic syndrome." It results from permanent occlusion of the axillary and subclavian veins by the organization of the thrombus. The severity of the residual symptoms depends

upon the degree of the formation of collateral circulation. As the acute process subsides, there appear newly-developed collaterals over the shoulder and upper arm, and the edema disappears (Figs. 2, 3). There are no further symptoms while the arm is at rest. Following exercise or prolonged use of the involved limb, the patient feels a sense of fullness, weakness, fatigue and actual pain in the arm and shoulder. In some cases there may be a recurrence of the edema following prolonged exercise.

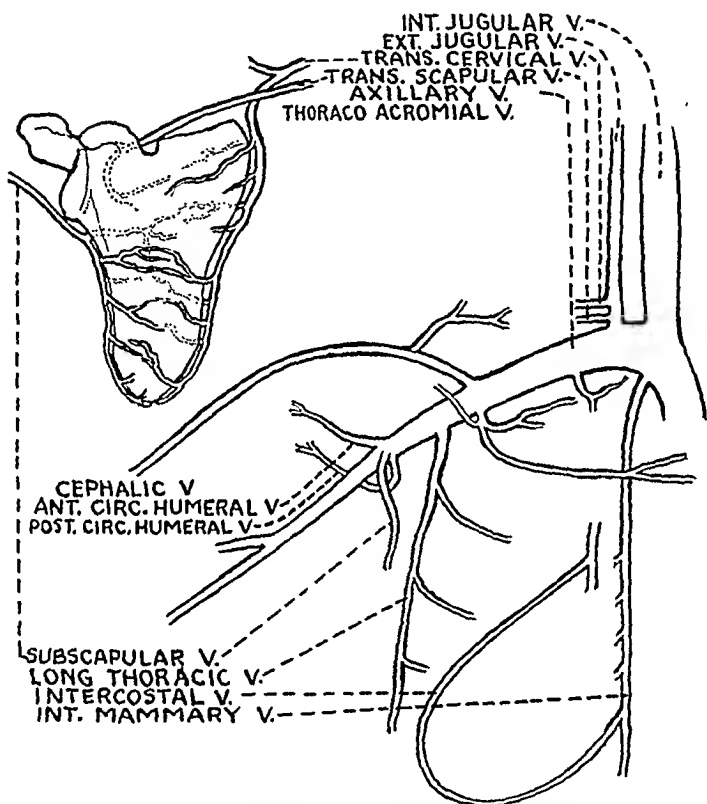


FIG. 6.—Possible routes through which collaterals may develop after obstruction of the axillary and subclavian veins.

There have been only scant reports of follow-up studies after the immediate convalescent or acute stage. However, in those reporting check-up examinations several months to several years after the onset, many have noted this post-thrombotic syndrome. Jeanency and Mathey-Cornat<sup>9</sup> found pain and swelling in the arm of a patient 6 years after onset of the thrombosis. Firth and Mackay<sup>6</sup> reported a case in which the right arm was involved and in which there was persistent pain after a hard day's work 2 years later. Two years after the onset of the edema in the right arm, the left arm became involved. Ballon<sup>1</sup> reported a case that had discomfort following exercise 20 months after the initial onset. In one of

Clute's<sup>5</sup> cases pain and swelling followed hard labor one year after onset. Baum<sup>2</sup> cited a case with persistent and recurrent edema one year and a half after onset.

In our series of 9 cases of phlebothrombosis and thrombophlebitis, 7 showed residual symptoms after recovery from the acute stage. Three were followed for only 2 months after the occurrence of the thrombosis. One was examined monthly for 6 months. The other 3 were observed at 22, 10 and 6 years, respectively. All 7 presented weakness, early fatigue and pain in the arm after prolonged work or exercise of the involved extremity.

Matas,<sup>12</sup> in an excellent communication on this subject, emphasized the importance of the residual symptoms and discussed the possible medico-legal aspects that may confront one in the management of such cases.

From the venographic demonstrations of the collateral circulation and the venous pressure changes noted in these cases, it seemed clear that the residual symptoms were due to the retardation of the return venous blood flow. Venous pressure studies in a large series of patients with axillary and subclavian vein obstruction following radical removal of the breast had shown that in those with persistent edema of the arm there was marked elevation of the local venous pressure. In this group the average antecubital vein pressure was 530 mm. saline. In one, the pressure reached the amazing level of 1400 mm. saline. In another group of these postoperative cases the patients exhibited edema of the arm only after prolonged exercise of the involved extremity. The edema would subside within 24 hours with complete rest and elevation of the arm. In these the local venous pressure during rest was uniformly lower than in the first group, and in some was within the normal range. It seemed that the collaterals were adequate during rest, but incapable of coping with the great increase in blood flow during exercise.

We then made a series of venous pressure determination on a selected group during active exercise. The antecubital vein was punctured and the pressure recorded at complete rest with the patient in the supine position. Then the patient was instructed to close the hand tightly and immediately release it while the venous pressure apparatus was still in place. This alternate closing and opening of the hand was carried on at a rate of about 30 per minute for a period of 1 to 3 minutes. It was found that during the exercise there was a steady rise in the venous pressure. On stopping the exercise there was a gradual return to pre-exercise level. The same experiments were then conducted on the opposite arm and in a series of normal individuals, and in none did the exercise cause a rise of more than 10 mm. saline. These experiments show that the residual symptoms that follow occlusion of the axillary and subclavian veins are due to the abnormal venous pressure (Chart 1).

The severity of these symptoms depends upon the extent of the

development of the collateral circulation. In some, the collateral venous channels may become adequate to take care of the return blood, and there will be no residual symptoms. In others, there may be sufficient channels to care for the venous flow during rest, but not capable of coping with the increase in flow which follows exercise. In these the exercise causes an increase in the local venous pressure, retardation of flow and lowering of oxygen content. As long as the exercise is continued there is a gradual damming back

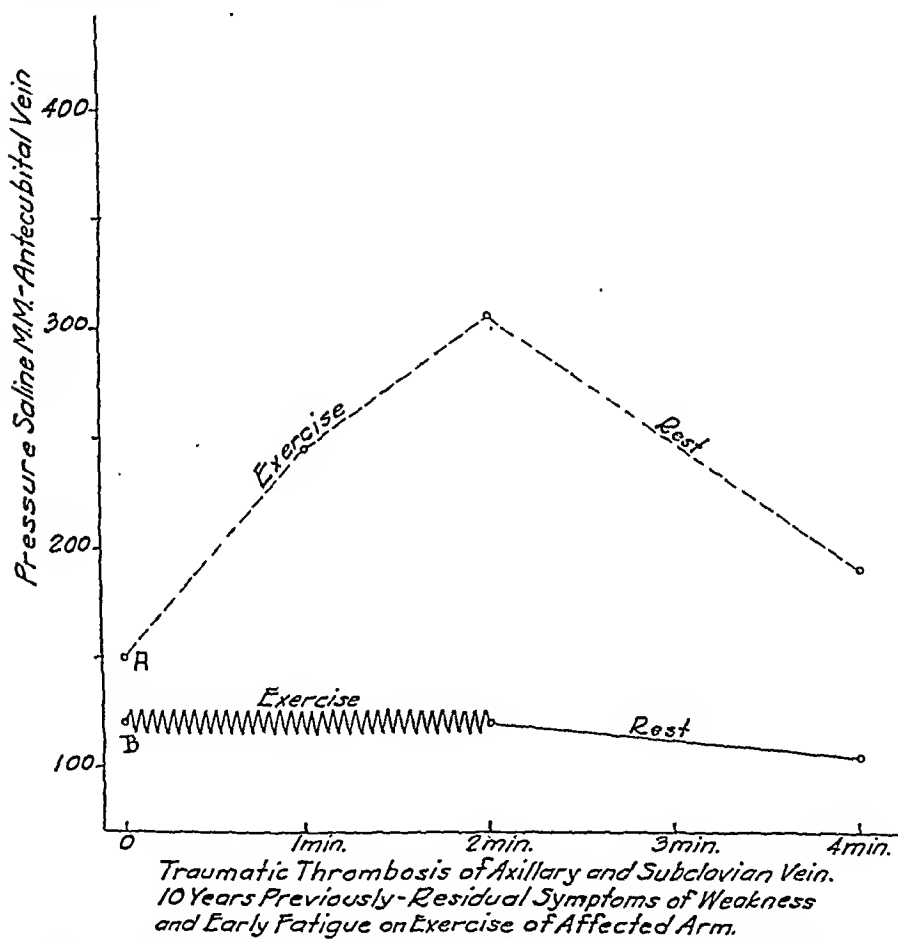


CHART 1.—Reaction of the local venous pressure to exercise in a case of permanent occlusion of the axillary and subclavian veins from phlebothrombosis—the post-thrombotic syndrome: A, Represents the venous pressure curve during exercise in the veins of the obstructed arm; B, The venous pressure curve, during exercise, in the veins of the normal arm.

of the venous blood under increasing pressure, thereby producing a sense of fatigue or weakness, pain, and finally edema. In still another group, even during rest, the venous pressure may be sufficiently high to cause persistent edema. In these, exercise, of course, elevates the pressure to an even higher level and causes an increase in the edema.



A presumptive diagnosis of axillary and subclavian vein occlusion can usually be made from an accurate history and careful physical examination. The diagnosis can be positively confirmed by means of venographs of the local venous circulation. We have previously described<sup>14b</sup> a simple method of directly visualizing the axillary and subclavian veins and will not repeat the technique in this communication. By such a method of study it is now possible to locate the point of obstruction, to demonstrate the extent of involvement and to visualize the remaining patent venous channels (Fig. 1).

A comparison of the venous pressure in the affected extremity with that in the normal arm provides additional information. In cases of swelling of the arm resulting from local venous obstruction, there is an elevation of the venous pressure in the involved arm, and normal in the opposite member. In cases of obstruction of the mediastinal veins there is an elevation of the venous pressure in both arms. In swellings of the arm not caused by venous obstruction, the venous pressure remains normal at rest and during exercise of the limb. Repeated venous pressure studies will also prove valuable in determining the progress in an individual case. Residual symptoms should be expected when the venous pressure remains elevated with the arm at rest, or shows an abnormal increase during exercise of the extremity.

**Treatment.** There are no known surgical measures that will completely relieve thrombosis of the axillary and subclavian veins. Surgical exploration has been undertaken in a few cases, but the end results do not seem to justify further attempts. In certain cases in which the thrombosis is extensive and in which there is an extreme degree of edema, multiple skin punctures may prove very helpful. This procedure must be done under strictly aseptic precaution. Thrombophlebitis and phlebothrombosis of the axillary and subclavian veins are best treated by complete rest, elevation of the extremity on soft pillows, and the local application of heat. Rest and elevation should continue until there is obvious development of collaterals. In practically all cases the edema will disappear within a few days to several weeks. There should be a gradual resumption of activities. The patient should be warned of the possible residual symptoms.

Thrombosis of the axillary and subclavian veins secondary to malignancies of the chest and axilla should be treated by rest and elevation of the arm. There is little hope of cure of the malignancy, but the effect of the local venous obstruction may be overcome to some degree by the formation of collaterals. The development of collateral venous circulation is a natural process. This process is retarded by conditions that increase the edema; it is aided by conditions that lessen venous congestion.

**Summary.** 1. The symptom complex of thrombosis of the axillary and subclavian veins is reviewed.

2. A classification and examples of the various types of thrombosis is given. Clinical studies from 17 cases are recorded.
3. The frequency of secondary thrombosis from malignancies of chest and axilla is emphasized.
4. The development of collateral circulation after occlusion of the axillary and subclavian veins is discussed.
5. An explanation of the post-thrombotic syndrome, based on the inadequate collateral circulation and elevation of the local venous pressure, is offered.
6. A résumé of treatment for the various forms of thrombosis is outlined.

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## THE MYOCARDIAL DEGENERATION ASSOCIATED WITH UREMIA IN ADVANCED HYPERTENSIVE DISEASE AND CHRONIC GLOMERULAR NEPHRITIS.

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THERE occurs in uremia an unusual type of myocardial degeneration that apparently has escaped the attention of pathologists and clinicians. It is seldom seen in purely "obstructive" uremia, but contrariwise, it is not uncommon in those patients who exhibit renal insufficiency associated with severe hypertensive disease. It has also been seen in some patients with chronic glomerular nephritis. This myocardiopathy\* is probably an important factor in the cardiac failure of uremia, a failure which we believe is rather frequent but often obscured by other aspects of the toxemia.

There are few references concerning the influence of uremia on the myocardium. Wood and White<sup>12</sup> reported on the electrocardiographic changes, directing attention to the existence of "toxic"

\* "Myocardiopathy" is used here in lieu of a more specific nomenclature that necessarily awaits a detailed knowledge of these unusual myocardial lesions.

effects that could not be ascribed to digitalis therapy or to common types of myocardial degeneration. Heitz<sup>5</sup> and Chaliér and Contamin<sup>2</sup> pointed out the frequency of pulsus alternans. Fishberg,<sup>4</sup> quoting these observations and certain personal experiences, believes that heart muscle may be directly injured by uremic toxemia. Only one report, as far as we know, deals with pathologic changes in the myocardium presumably due to uremia. Lüscher<sup>7</sup> described a severe interstitial hemorrhagic myocarditis in a nephritic patient, which was histologically identical with idiopathic interstitial myocarditis (Fiebach,<sup>3</sup> Sellentin<sup>11</sup>).

The lesions herein described are different from those ordinarily seen with heart disease. They were found in 34 uremic and pre-uremic patients whose clinical course and necropsy findings form the basis of this report.

Aside from hypertrophy of the heart, there is often in uremia a flesh-colored mottling of the muscle, usually most marked in the posterior and lateral walls of the left ventricle (Fig. 1). Section reveals yellowish-gray, buff, or occasionally pale salmon-colored foci of myocardial degeneration, usually having a uniformly smooth appearance. The cut surface is rather dry and slightly swollen, suggestive of some form of coagulation necrosis. A resemblance to firm suct may be noted. These foci vary greatly in size and shape, some being of millet-seed size, others so large as to occupy as much as one-half or more of the thickness of the ventricular wall (Fig. 2). In many instances they are fairly well demarcated, sometimes appearing as wedge-shaped lesions extending down from the epicardium into well-preserved myocardium. Often, however, this demarcation is indistinct, the lesions gradually merging with widespread degenerative changes of a similar nature, only less pronounced. The more striking color changes of acute myocardial infarction are not present, nor is any focal softening, mural thrombus, or any gross fibroblastic reaction demonstrable. These peculiar lesions of uremia apparently show a preference for the outer (subepicardial) zone of the posterior and lateral walls of the left ventricle (Fig. 3). They often collect under the epicardium, through which, in the absence of pericarditis, they are easily seen. However, they may be found in any part of the heart, *e. g.*, in the papillary muscles, and are often scattered irregularly in the walls of the right ventricle and auricle. In two instances we noted marked degenerative changes in the area of the sino-auricular node which were probably the basis for interesting electrocardiographic changes. The left auricle is not involved as often as other areas.

The overlying epicardium often shows a hyperemia which occasionally is so intense as to give a scarlatiniform appearance to the heart (Fig. 1). With changes of such degree the normal epicardial sheen may be lost, suggesting an oncoming pericarditis. The myocardial lesions on the freshly cut surface often become temporarily

more pronounced. Their color quickly fades in fixative solutions containing formalin, as does the color of all of the myocardium in cases of uremia. (Klotz No. I solution, frequently renewed, is a fairly satisfactory preservative.)

The above description applies to focal lesions easily recognized in many instances because of their location and their appearance. However, many hearts from uremic patients who had signs of cardiac failure did not show these lesions. Instead, the hypertrophied myocardium, which in the hypertensive state is usually firm and beefy red, was pallid, sometimes pale red or yellow-gray, and while generally firm, its cut surface had a swollen greasy appearance. The fascicular markings of the cut surface were usually lost. This degeneration was in some instances limited to a rather broad belt of muscle beneath the epicardium, suggestively confining itself to a particular layer of the myocardium. The papillary muscles in such instances were often concurrently involved. In other cases, the entire wall of large portions of the left ventricle showed the greasy pallor, the swollen cut surface and loss of fine muscle markings noted above. Occasionally, in such widespread degenerative changes a more intense focal subepicardial involvement could still be traced. We believe that these widespread changes are identical with the focal lesions described above, differing only in scope and severity.

**Association of Pericarditis With Uremic Myocardopathy.** In 7 of the 34 cases gross pericarditis was present. In 6 instances it was of the typical uremic type, the exudate consisting of a thin deposit of glistening "frosty" fibrin, easily removed from an almost smooth but hyperemic epicardial surface. In the seventh case, a 14-year-old girl with chronic glomerular nephritis, the pericardial reaction was older (subchronic), with widespread adhesion. More common than grossly demonstrable pericarditis was a variable degree of hyperemia usually over those areas where the myocardial lesions were most pronounced. Its occasionally intense red appearance has been mentioned above. Uremic pericarditis was not seen in the absence of myocardial degeneration whether the latter was focal or of the diffuse type. It is therefore our impression that pericarditis is in most instances a complication of the myocardopathy, probably a result of the same "toxic" process.

**Histopathologic Changes in Uremic Myocardopathy.** The histological picture is usually less striking than the gross changes would indicate. The microscopist, mindful of the well-demarcated gross lesion that suggested focal necrosis, will be disappointed in finding merely a vacuolization due to fatty degeneration (Fig. 4), or else a hazy swelling of myocardial fiber (Fig. 5), or both of these changes. However, closer inspection indicates that this fatty degeneration differs from other types of such degeneration. The tendency to subepicardial rather than subendocardial localization as seen in

"tabby cat" or tigroid fatty degeneration is interesting. It should be noted, of course, that this subepicardial localization is relative and not absolute; the degeneration may be seen throughout. Possibly similar subepicardial degenerative changes are seen in other disease states, especially in association with pericarditis, but they are not so striking. The fatty vacuolization in uremic myocardial degeneration is usually very fine. It may be so small as to escape notice in routine examination, or it may be difficult to differentiate from hydropic vacuolization. Fat staining with Sudan III often yields a very fine red stippling, as if Cayenne pepper had been dusted over the section (Figs. 6 and 7). In advanced degenerations larger droplets of fat are also numerous, but seldom is the vacuolization as marked as in pernicious anemia or in the degenerations of some infections (diphtheria, occasionally acute rheumatic fever). In some instances the vacuolization gives a very fine moth-eaten appearance to each fiber (Fig. 4).

Other histologic features are hyaline degeneration and a tendency to marked swelling of the muscle fibers. The latter are often so increased in size as to diminish greatly the interstitial space in many

#### LEGENDS FOR FIGS. 1 TO 11.

FIG. 1.—Uremic myocardiopathy; flesh colored subepicardial foci of myocardial degeneration (X), distinct from the epicardial fat (Y). Note congestion (dark) of the adjacent epicardium. Insert at lower corner shows tangential section through mottled areas. From a patient, aged 46 years, with cardiac failure and uremia. (Photography by Gosner, Philadelphia General Hospital.)

FIG. 2.—Advanced uremic myocardiopathy without pericarditis; tangential section, left ventricular wall. Malignant hypertension, cardiac failure, moderate azotemia.

FIG. 3.—Uremic myocardiopathy; note subepicardial localization, marked congestion in overlying pericardium and early pericarditis. Woman, aged 63, with paroxysmal dyspnea and ankle edema of 3 weeks' duration; B.U.N. 230 mg. per 100 cc. (Courtesy of S. Bellet and T. M. McMillan.)

FIG. 4.—Advanced fatty degeneration, uremic myocardiopathy. Note fine "moth-eaten" vacuolization. From focal subepicardial lesion (see Fig. 1.) (X 207.)

FIG. 5.—Swelling and foggy obscuration of myocardial fibers; early fatty degeneration; apparently earlier phase of degeneration (see Fig. 1). (X 253.)

FIG. 6.—Fat stain (Sudan III) showing advanced fatty degeneration in a focal subepicardial lesion (see Figs. 1 and 4).

FIG. 7.—Diffuse fatty degeneration of the myocardium (common type) in uremia. Note fine but almost universal stippling (Sudan III).

FIG. 8.—Hyaline swelling and early fatty degeneration; transitional changes in same field (X 207). Vines stain; man, aged 38 years, with blurred vision, vomiting, and blood pressure 284/176. Palpitation, moderate dyspnea, but no edema. T waves flattened in all three standard electrocardiogram leads. B.U.N. 150 to 220 mg. per 100 cc. Death in uremic coma.

FIG. 9.—Acute focal calcification, uremic myocardiopathy; a rare lesion. Note adjacent myocardial degeneration; man, aged 49 years, with dyspnea, hemoptysis, and malignant hypertension. B.U.N. 240 mg. per 100 cc.

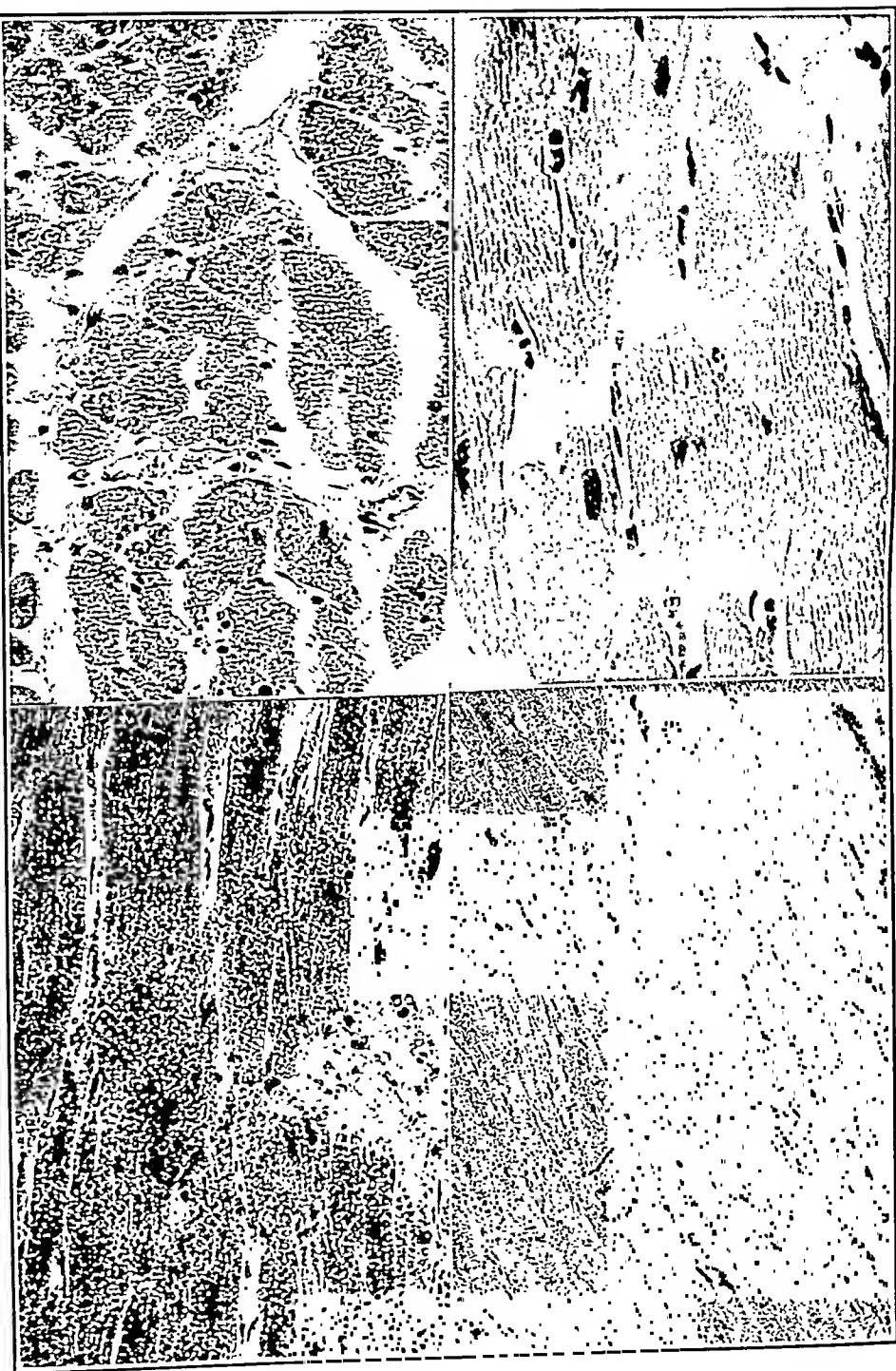
FIG. 10.—Marked degeneration of the sino-auricular node in uremic myocardiopathy. A, The artery of the S-A node; B, normal auricular muscle. Arrows mark the border of the degenerated, poorly stained node. From a patient with uremia, cardiac failure, bradycardia, and nodal rhythm (X 69).

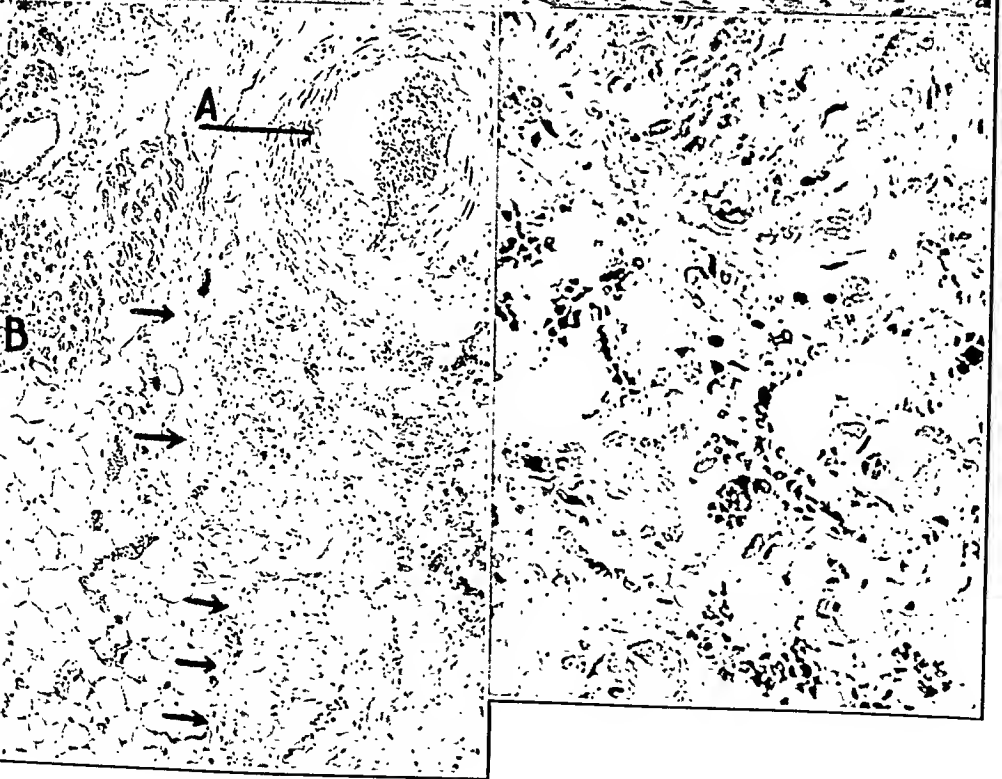
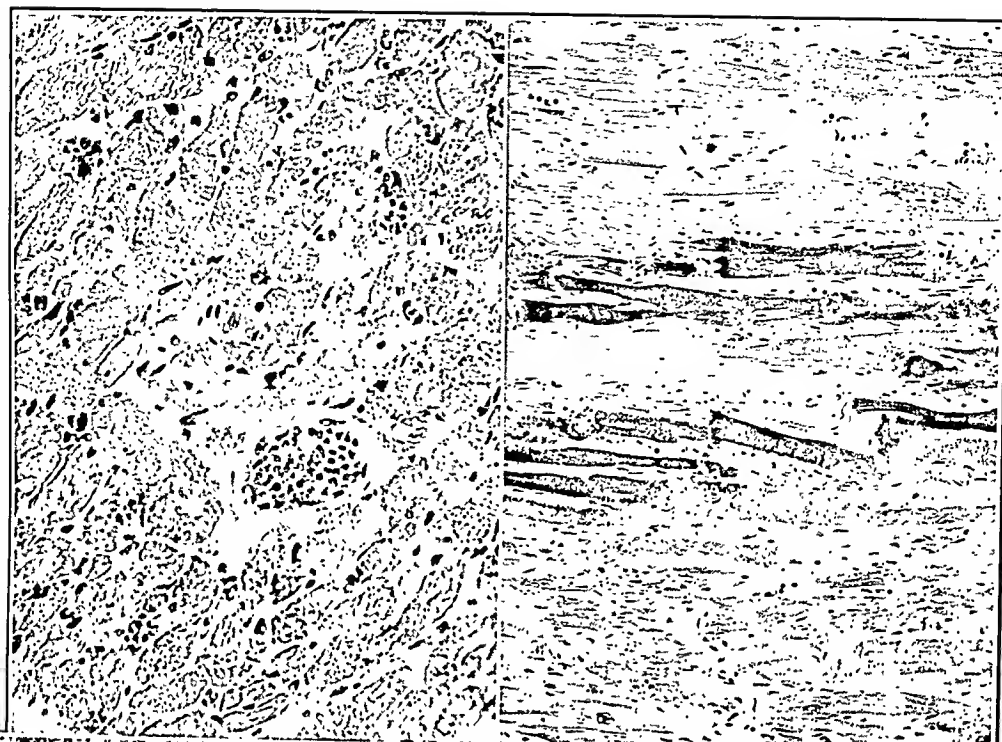
FIG. 11.—Marked degeneration in the S-A node; the nodal fibers, normally small and irregularly disposed, are here so degenerated, diminished in size, and so poorly stained as to be barely visible. Note the hemorrhagic infiltration.



METRIC SYSTEM 2 3 4 5











areas (Fig. 5). This swelling exceeds any enlargement due primarily to cardiac hypertrophy. With it there is often a foggy obscuration so that sharpness of detail is lost, not only of striation, but even of the actual outline of the fibers. In this fogginess the swollen fiber may present some appearance of homogeneity suggestive of an acute hyalinization (Fig. 8). Some stains (Vines) show this to better advantage than the routine hematoxylin-eosin. These changes, hazy swelling and hyalinization, apparently precede the fatty degeneration, which in some instances was only slightly or moderately developed when death occurred. Occasionally most of the sarcoplasm has disappeared, the fibrillæ being small and broken and replaced by a myxomatous type of edema.

We have noted one instance of acute focal calcification in association with this myocardiopathy (Fig. 9). Fishberg<sup>4</sup> cited a case of chronic glomerulonephritis in a young woman whose myocardium was the site of focal calcification. These two interesting cases possibly have a similar pathogenesis.

There is usually little or no cellular infiltration. In some cases, scattered monocytes and an occasional neutrophil or eosinophil are noted. We have seen in only 2 instances in this series of 34 patients what might be termed a moderate degree of cellular infiltration. In conformity with standard nomenclature, the term "uremic myocarditis" would therefore not be truly acceptable.

**The Coronary Arteries and Arterioles.** The coronary arteries show a variable, occasionally considerable degree of atherosclerosis. This usually consists of discrete deposits of atheroma with yellow discoloration of the intimal surface. Advanced arteriosclerosis with fibrotic and calcareous degeneration leading to a serious degree of stenosis or actual occlusion of main coronary branches was seldom seen. In one instance, advanced stenosis of the right coronary artery was associated with a small organizing posterior myocardial infarction which was distinct in its appearance from the surrounding lesions of uremia. In practically all other cases the coronary arterial system appeared to be satisfactorily patulous and in many instances the arteries were not only surprisingly free of gross pathologic change, but were larger than normal, suggesting a compensatory increase of capacity in keeping with the cardiac hypertrophy.

Microscopy confirmed the usually good and often excellent gross appearance of the large arteries, but revealed a common incidence of arteriolar sclerosis. This, however, was uneven (segmental) and generally of mild degree. The usual findings were hyaline degeneration of the media and eccentric thickening of the intima seldom giving the impression of significant narrowing. Actual arteriolar necrosis (fibrinous necrosis), acute thrombotic closure and "onion-peel" hypertrophy of the media were not seen, although they were commonly present in the kidneys of the same patient. The capillaries were often distended, containing many erythrocytes. When

myocardial swelling was marked, the adjacent capillary bed was largely obliterated.

**The Clinical Aspects of Uremic Myocardiodiopathy.** This group of 34 patients, consisting of 17 men and 17 women, varied in age from 18 to 72 years; 21 were in the third, fourth and fifth decades, 9 in the sixth. There were 23 negroes and 11 whites. Our data are insufficient to be of value in tracing any familial tendency.

The large majority of these patients had severe hypertension. The systolic pressure generally was above 200 mm. mercury; the diastolic ranged from 120 to 140 and occasionally was as high as 180 mm. Eye-ground examination of 16 patients revealed in all a varying degree of the angiospastic and hemorrhagic changes of hypertensive disease. The age level, the high diastolic pressures, the rather rapid clinical course and the severe renal vascular damage that later was regularly found placed most of these patients in the classification of malignant hypertensive disease. Two of them were finally considered to be cases of chronic glomerular nephritis.

The patients could be separated into two groups: those with easily recognized heart failure, and those in whom the early presence of dyspnea was obscured by various complaints suggestive of toxemia, such as amblyopia, severe headache, vomiting, purpura and psychosis. In this latter group, the attending physician easily recognized the presence of uremia or of hypertensive encephalopathy. Dyspnea, which in many cases antedated the other symptoms, persisted and in some instances was accompanied by progressive edema, all of which was thought to be merely incidental to the progress of uremia. However, the patients in the first group were invariably regarded as victims of hypertensive cardiovascular disease with myocardial failure due to coronary arteriosclerosis. Dyspnea, palpitation, edema, gallop rhythm and bloody sputum were prominent features indicative of cardiac strain and decompensation. Other occasional signs and symptoms, possibly suggestive of uremia, assumed a secondary importance and the true clinical status was established only when laboratory reports revealed the presence of advanced renal insufficiency and serious azotemia. This state in which cardiac failure was the preponderant clinical feature lasted for a variable time, often for 2 or more weeks, and was prolonged in two instances for 3 months, the azotemia remaining at high levels. Usually there was an increasing mental dullness which finally ended in coma if life persisted long enough despite the circulatory failure. Often both advanced heart failure and coma were present in the terminal stage. Heart failure in the majority of cases was predominantly of the left ventricular type, death following extreme dyspnea and pulmonary edema. In others, failure gradually became generalized, accompanied by swollen liver, engorged neck veins and peripheral edema. Right heart failure was constantly predominant in only one patient. The hyperten-

sion persisted usually to almost the last day of life, regardless of the extent of circulatory failure. In a few there was a terminal drop, seldom, however, below 150 mm. systolic and 100 mm. diastolic. Arrhythmia was uncommon and no instance of systemic embolism was recorded. Two cases of left heart failure were complicated by pulmonary infarction, which could only be considered incidental to the intense passive hyperemia of the lungs.

Cardiac murmurs were fairly frequent, always systolic, and usually heard in both aortic and mitral areas. They were almost all functional, as revealed by necropsy, and could be ascribed to ventricular dilatation or anemia. Gallop rhythm was heard in 6 patients; it was of the ominous type—apical, presystolic, and associated with left ventricular enlargement. Pulsus alternans was either seldom recognized or else not present to the extent claimed by other observers.<sup>2</sup> Cardiac rates as high as 125 per minute were seen in some patients on admission to the hospital in the midst of acute left heart failure. They gradually were reduced as a result of bed rest and possibly digitalis therapy, and then usually remained between 70 and 100 despite the presence of dyspnea and increasing azotemia until shortly before death. There were 3 patients with bradycardia (rates, 52–65). Bradycardia has occasionally been noted in uremia.<sup>6</sup> While comparatively uncommon, the association is, we believe, authentic and is based, at least in some patients, on degenerative changes in the right auricle involving the sino-auricular node (Fig. 10). Wood and White<sup>12</sup> in their electrocardiographic study found 3 instances of sino-auricular block.

*Laboratory Data.* Urinalysis in practically every case showed low and fixed specific gravity coupled with a varying degree of albuminuria. In 28 patients the blood urea nitrogen was elevated above 60 mg. per 100 cc.; in most of these it ranged from 100 to 250 mg. per 100 cc. Of the 6 remaining patients, 2 died before blood chemistry studies were completed. Four patients who will be discussed later had only moderate azotemia, the blood urea nitrogen being 32 to 50 mg. per 100 cc. In 3 of these 4 patients, urea clearance tests pointed to renal insufficiency. Creatinin retention was present in each of 21 patients, ranging from 3 to 18.5 mg. per 100 cc.

The varying degree of anemia usually associated with uremia was noted in this group. Some erythrocyte counts were as low as 2,500,000, and in one instance, 1,800,000. The majority of patients had 3,500,000 or more; a few had close to 5,000,000 erythrocytes; but in such instances vomiting and hemoconcentration were possibly important factors.

The degree of acidosis likewise varied greatly. The CO<sub>2</sub> combining power was determined in only 7 patients, of whom 3 showed no diminution, 2 a moderate diminution, and 2 a marked acidosis (17 vol. %).

The Wassermann reaction was positive in 5 patients. It appeared to be an incidental finding, since no clinical or pathologic evidence of syphilis was found in any case.

*Electrocardiographic Studies.* In 18 patients there were 12 instances of left axis deviation. Arrhythmia was relatively uncommon; 1 patient had nodal rhythm; 2 others with bradycardia were not studied electrocardiographically. One patient developed auricular fibrillation and 3 instances of ventricular extrasystoles were noted.

*T-wave changes and deviations of ST intervals* from the isoelectric line were common. Flattening or inversion of *T1* and *T2* in combination was noted 6 times; of *T2* and *T3*, once; of all 3 *T* waves (indirect leads), 4 times. Depression of *ST* in Leads 1 and 2, twice; of *ST2* alone, 4 times. The chest leads showed no unusual changes in the absence of pericarditis.

*Occasional Findings.* Large *S* wave in Lead 2 and also prolongation of *QT*, twice; the latter has been noted in connection with hypocalcemia common in uremia.

Thus numerous deviations from the normal electrocardiographic pattern were noted. Undoubtedly some of them were due to uremia, as suggested by Wood and White.<sup>12</sup> We believe, however, that only a detailed analysis beyond the scope of this report can estimate the significance of the electrocardiographic changes. Many factors are involved; for example, Bellet and McMillan<sup>1</sup> have demonstrated that some of these changes are due to pericarditis.

*Dyspnea, Edema and Absence of Angina Pectoris.* Certain clinical features are worthy of further comment. Dyspnea was present in every case, usually from the beginning. Many patients were incapacitated by paroxysmal dyspnea, while others became aware of a very slowly developing shortness of breath that continued for many weeks, occasionally for as long as 3 or 4 months. In some instances, a respiratory infection appeared to initiate this subtle cardiac failure. Dyspnea was undoubtedly aggravated by the acidosis common in uremia, but its cardiac origin nevertheless was clearly evident in the history and concomitant physical signs in every case. It did not differ, except terminally, from the dyspnea seen in other types of heart disease.

Edema developed in the majority of these cases, but it was variable in degree and in the time of its appearance. While many patients eventually became markedly edematous, others developed only a moderate degree of ankle edema shortly before death and occasionally edema was conspicuously absent. Pulmonary edema was, of course, usually present. In some patients, not only the absence of peripheral edema, but actual dehydration was striking, contrasting with evident cardiac decompensation as indicated by recurring pulmonary edema, gallop rhythm, and a moderate venous hypertension. Possibly polyuria secondary to renal tubular atrophy

is a determining factor in the relatively "dry" type of heart failure seen in some uremic patients.

In contrast to the constant presence of dyspnea and the appearance in the majority of some degree of edema, angina pectoris and precordial pain were absent in all but 2 uncomplicated cases. Chest pain occurred with the onset of pericarditis and also appeared in the history of 2 patients who at necropsy had no structural basis for it except cardiac hypertrophy and uremic myocardiopathy. The common absence of an anginal syndrome is interesting when one considers the usual degree of ventricular hypertrophy and the persistently severe hypertension in these cases. Sensitivity to pain is probably diminished in uremia. Nevertheless, pain was present in 4 of the 6 patients with acute pericarditis, a complication that occurs usually near the end of life when mental impairment is evident. The absence of serious occlusive coronary artery disease may be of some importance in this picture of painless myocardiopathy.

Abstracts of the clinical findings in 2 patients are herewith presented:

**Case Reports.** CASE 1.—C. M., negro male, aged 45, was admitted to the Philadelphia General Hospital (service of Dr. F. J. Kalteyer) complaining of shortness of breath and cough. In July, 1937, he became weak, short of breath, and began to cough with blood-streaked sputum. No chest pain was felt, but recently he was conscious of rapid heart action and palpitation. Past medical history was irrelevant. Examination revealed a mentally confused, dyspneic negro, with cardiac enlargement, râles at both lung bases, distended neck veins, and enlarged liver. The blood pressure was 225 mm. systolic, 155 diastolic. The B.U.N. varied between 110 and 140 mg. per 100 cc.  $\text{CO}_2$  was 62 vol. %. Red blood cell count was 3,500,000. Digitalis therapy and intravenous sucrose injections were of no value. The patient developed Cheyne-Stokes respiration, and after lapsing into coma, died on Oct. 8, 1937.

CASE 2.—A. P., a colored woman, aged 53, was admitted to the Philadelphia General Hospital (service of Dr. Robt. Torrey), July 3, 1937, complaining of shortness of breath which, while present in mild degree for possibly a year, became very marked in the last 5 weeks. It was accompanied by leg edema, but there was no precordial pain. The amount of urine was progressively less in recent days.

Examination revealed an obese woman with Cheyne-Stokes respiration. Eye-ground examination showed advanced "albuminuric" retinitis. The blood pressure was 220/110, the neck veins were prominent, and a few râles were heard at both bases. The heart was enlarged to the left and a presystolic gallop rhythm was heard in the apical area. Occasional extrasystoles were heard, but the cardiac rhythm was otherwise normal, rate 80 per minute. The liver was slightly enlarged and there was moderate leg edema. On July 6, convulsive seizures suggestive of hypertensive encephalopathy occurred, during which severe pulmonary edema developed, terminated finally by death. Laboratory examination for determination of azotemia had not been completed, but necropsy revealed typical lesions of necrotizing arteriolar nephrosclerosis and uremic myocardiopathy. The coronary arteries, slightly atheromatous, were widely patent, actually enlarged throughout.

**Discussion.** While small focal lesions, possibly similar in type to those herein described, are occasionally found in hearts of non-hypertensive individuals, the well-developed gross changes represent, we believe, a myocardial degeneration characteristic of malignant hypertensive disease or of chronic glomerular nephritis in which uremic or pre-uremic states have been reached. We have included the term "pre-uremic" because, while the large majority of these patients had marked azotemia, 4 of them showed it only to a moderate degree. Of the latter, 1 patient had left heart failure for 2 months, associated with persistently high blood pressure, and a blood urea nitrogen level of 42 mg. per 100 cc. Necropsy revealed the myocardial degeneration of uremia and the renal lesion of malignant nephrosclerosis. A second case died with hypertensive encephalopathy, complicated, however, by left ventricular failure. The third case, a woman, aged forty-eight years, with marked diastolic hypertension, was hospitalized with left heart failure. The existence of advanced renal sclerosis was considered likely on the basis of the eye-ground changes and the fixed low specific gravity of the urine. However, the blood urea nitrogen was only 34 mg. per 100 cc. While under observation, the patient developed hypertensive encephalopathy. Later, both the cardiac and mental states improved with the concurrent disappearance of the moderate azotemia. Within 6 weeks, cardiac failure of the "dry type" and encephalopathy recurred, associated with a rise in blood urea nitrogen to 32 mg. per 100 cc. Death followed recurring paroxysmal dyspnea and pulmonary edema. Necropsy revealed the typical uremic myocardiopathy and brain changes that are associated with hypertensive encephalopathy.<sup>9</sup> In the fourth case, azotemia had apparently receded from a higher level, yet clinically there was increasing evidence of cardiac decompensation and toxemia. At necropsy, the myocardial damage was extensive. It thus appears that the myocardial changes are not absolutely dependent on the presence of severe azotemia, although most often are seen with it. Rather, they suggest a "toxic" effect in the hearts of some hypertensive patients who suffer from a progressive poisoning which culminates in uremia. This course is sometimes interrupted by the development of encephalopathy.

The myocardiopathy is in our experience a common occurrence. We have no exact figures but believe it can be seen in the majority of the uremic patients who exhibit signs of heart failure, other than the immediately terminal failure commonly seen in the last few hours of life. The high incidence in negro patients is due to the comparatively large colored population at the Philadelphia General Hospital, and the greater frequency of severe hypertensive disease in the negro race.<sup>8,10</sup>

The pathogenesis of this degeneration is undetermined. The

importance of anoxemia has been emphasized in many circulatory disease states and two conditions favor its development in hypertensive and renal disease, namely, arteriolar sclerosis and anemia. Myocardial arteriolar sclerosis was often present, but its non-necrotizing character has been noted by others as well as ourselves.<sup>4</sup> The possibility of arteriolar spasm cannot be ignored. However, the absence of ischemic necrosis and of widespread fibrotic replacement suggests that this myocardial degeneration is not entirely due to occlusive vascular disease. Moreover, such degeneration has not been seen in advanced emphysema, in chronic coronary artery insufficiency, or in cases of syphilitic aortitis complicated by almost complete stenosis of the orifices of the coronary arteries, examples of cardiac involvement in which anoxemia supposedly plays an important rôle. Finally, in this connection, the slight incidence of angina pectoris should not be forgotten. We believe that anoxemia is at the most only a contributing factor.

The degree of anemia varied greatly and thus no definite conclusion could be drawn as to its importance. Pallor of the myocardium is generally present with marked anemia; yet often, the diffuse as well as the focal uremic degeneration was present in patients with erythrocyte counts above 3,500,000. The same lack of parallelism was seen in reference to acidosis. While these factors cannot be disregarded, none of them can be accepted on the basis of the accumulated data as the major cause of the myocardial pathology. We believe that the lesions are a result of the action of a "toxin," the nature of which is part of the secret of uremia.

**Summary.** A peculiar type of myocardial degeneration appears to be intimately associated with the uremic and pre-uremic states of arteriolar nephrosclerosis and chronic glomerular nephritis. It is found especially in those patients who have cardiac failure. The latter may be the outstanding feature of uremic intoxication. Pericarditis may be regarded as a complication of this myocardial pathology.

We are indebted to the chiefs of service, both medical and laboratory, for the privilege of utilizing the clinical and pathologic material at the Philadelphia General Hospital in the preparation of this report.

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## THE RELATIONSHIP OF MIGRAINE TO HYPERTENSION AND TO HYPERTENSION HEADACHES.

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THE majority of patients who have hypertension are subject to headache at one time or another and frequently it is the initial complaint. In 1913, Janeway<sup>1</sup> observed that his patients who had hypertension complained of headache as their most frequent symptom. He found that evaluation of the rôle that hypertension played in producing these headaches was difficult, as a large number of these patients had been subject also to migraine at some time during their lives. In recent years, those who have been interested in hypertension have likewise noted its frequent association with migraine. These observations have been made casually and as far as we know, a previous attempt has not been made to establish such a correlation statistically. It is for this purpose that the present study was undertaken.

The characteristic features of a migraine headache are the periodic nature of the attacks of pain that are confined to one side of the head (hemicrania) and associated visual disturbances, especially scotomas, and nausea and vomiting. There may be a wide variation from the typical description although the more the symptoms vary from the classic symptoms the less likely is the headache to be a true migraine. Some common variations observed are the absence of hemicranial limitation of the pain and the absence or minimal nature of the visual and gastric disturbances. In almost all cases of true migraine, however, the patient will have had one or several attacks, at one time or another, that are associated with visual and gastro-intestinal disturbances. The attack may last from one to several hours or days.

The headache usually considered to be most frequently associated with hypertension is the so-called typical hypertension headache; that is, one which is present when the patient awakens, or which awakens him during the early morning hours. It reaches its greatest intensity before breakfast and disappears after breakfast or during the early morning. The headache is usually occipital but may occur in any part of the head. Seldom is it unilateral. It may vary from a dull ache or feeling of pressure to a severe bursting or throbbing pain. Visual, auditory or other aura may precede the headache and nausea and vomiting may accompany it, thus giving some resemblance to migraine. However, these phenomena are rare.

**Method of Study.** One hundred patients who had been seen in consultation at the clinic because of hypertension were carefully questioned by us as to the presence of migraine or a previous history of migraine. These patients were seen consecutively and no attempt was made to select them. All had a systolic blood pressure of more than 160 mm. of mercury and most of them had one or more symptoms usually associated with hypertension. We also noted the presence of other types of headache and the change, if any, that had occurred in the migraine headache, if such had been present before the hypertension was discovered. All patients were questioned as to the family history of both migraine and hypertension. The age of the patients varied from 20 to 65 years; the large majority falling between the ages of 40 and 60 years. There were 38 men and 62 women.

In order to have a control series to compare with the group of cases of hypertension, a second study was made on a series of 100 patients who had normal blood pressure. These patients were selected at random from routine admissions to the clinic. The same care was exercised in eliciting a history of migraine from the patients of this group. The ages of these patients were between 40 and 60 years. Sixty of the group were women and 40 were men. The general preponderance as to age and sex thus compared favorably with those of the hypertension group.

**Result of Study.** *The Association of Migraine with Hypertension.* A surprisingly large number (79%) of the group of patients who had hypertension admitted either that they were subject to migraine at present or had had such attacks in the past. In the control group there was an incidence of migraine of only 15%. This compares closely with an incidence of migraine of 18% as found by Traut and Vrtiak<sup>2</sup> in their control group in a study of allergy in cases of arthritis. Fifty-six patients, a majority of those seen, indicated that they were still troubled with migraine to a variable degree despite the onset of hypertension. The presence of hypertension had been accompanied by no change in the symptoms of migraine of 31 patients; the number and severity of the attacks of migraine had decreased in 17 and had become accentuated in 8 cases.

It is interesting to note that in the total registration at the clinic during 1938, the diagnosis of migraine was recorded approximately 5 times as frequently in the group in which a diagnosis of hypertension was also recorded as in the group in which the diagnosis of hypertension was not recorded. The incidence was 7.7% and 1.6%, respectively.

*The Association of Migraine with Hypertension Headaches.* As has been previously stated, it is known that many patients who have a high blood pressure experience the development of the so-called hypertension type of headache. Of the 100 patients who had hypertension and who were studied, 44 complained of a hypertension type of headache. Of the 79 patients who had migraine, 38 (48%) experienced the development of a hypertension type of headache also, but of the 21 patients who had not had migraine, only 6 (28%) experienced the development of a hypertension type of headache.

Twenty-three of the 79 patients who had related a history of migraine were troubled no longer with this complaint at the time

when they had hypertension. Seventeen (69%) of these, however, had experienced the development of the hypertension type of headache. Of the 56 patients whose migraine persisted after the onset of hypertension, 21 (37%) also had experienced the development of a hypertensive type of headache, thus having attacks of headache characteristic of both disease processes.

*Incidence of Family History of Migraine and Hypertension.* Only 23% of the group of patients who had hypertension gave no family history of migraine or hypertension. Of the 79 patients who had associated migraine, 37 (approximately 46%) gave a history of migraine in their respective families, and of the 100 patients who had hypertension, 67% gave a family history of hypertension and 43% gave a family history of both migraine and hypertension. Of the 21 cases in which no migraine was associated, only 2 (approximately 10%) gave a history of both migraine and hypertension. Thus, it would seem that the association of migraine and hypertension is intimately concerned with hereditary factors common to both conditions.

*Relationship of Age and Sex to Migraine and Hypertension Headaches.* The incidence of migraine was approximately the same in both men and women. Approximately 40% of the 42 patients who had hypertension and who were more than 45 years of age no longer had migraine as compared with only 17% of the 37 patients who were less than 45 years of age. This would indicate that age, rather than the onset of hypertension, was the factor in the relief of the migraine. It is interesting that of the group of patients who had migraine, the men were much more likely to experience the development of hypertension headaches than the women by a ratio of about 2:1.

*Comment.* One cannot follow a number of patients who have hypertension without being impressed by the frequency with which migraine or the history of previous migraine occurs in association with hypertension. That this clinical impression is well founded is borne out in this study in which it was observed that migraine occurred approximately 5 times as frequently among patients who have hypertension as it does among individuals who do not have hypertension. The remarkable frequency of this association cannot be overlooked. On the other hand, the significance of such a relationship is not readily apparent. It is probable that a common factor in the pathogenesis of the two conditions is intimately concerned with their close association. The importance of a vascular factor in the production of attacks of migraine is now well known and there is considerable evidence that vasoconstriction plays an important rôle in producing the attack of migraine as it does in the production of hypertension. The common factor in the two conditions may be influenced by genetic factors which particularly concern the inheritance of a certain type of personality. Wolff's<sup>3</sup>

characterization of the person who has migraine as a person who has unusual ambition, who is meticulous and exacting, and who is a hard driver with the ability to accomplish much in a short time is certainly typical also of the personality of the patient who has hypertension. The close association of migraine with the development of a hypertension headache is also noteworthy. A certain number of patients studied were noted to have recovered from attacks of migraine before or at the time of onset of their hypertension. It seems unlikely that the onset of hypertension was the cause of the cessation of migraine, in view of the fact that a greater number of individuals retained symptoms of migraine in spite of the presence of hypertension. Some of these, moreover, were found to have experienced the development of hypertensive headaches and some were prone to have attacks of either type. Finally, our results tend to indicate that of all individuals who experience the development of high blood pressure, those who previously had had migraine are more likely to experience a hypertensive type of headache as one symptom of the hypertension than those not so afflicted.

**Summary.** Migraine occurs approximately 5 times as often in a group of patients who have hypertension as in a group of non-hypertensive patients of corresponding ages. The association of migraine with hypertension is probably influenced by genetic factors. Some patients experience a cessation of attacks of migraine prior to or coincident with the development of high blood pressure. This seems to be related more to the advancing age of the patient than to the onset of hypertension. Individuals who no longer have migraine headaches frequently experience those of the hypertension type. Those who retain their migraine are likely to have both types severely. An individual who has migraine is more likely to experience the hypertension type of headache than one not similarly afflicted.

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### DIABETIC CONTROL VERSUS CALORIC SUFFICIENCY IN THE TREATMENT OF DIABETES AND PULMONARY TUBERCULOSIS.

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THE peculiar susceptibility of the diabetic to tuberculosis has excited the interest of clinicians for hundreds of years. Indeed, Aretaeus not only gave a clear and comprehensive description of

pulmonary tuberculosis, but also defined and described diabetes mellitus in the second century, A.D.

Primary infection depends upon contact, and is no more frequent in diabetics than in non-diabetics. This is clearly indicated by skin tests in young diabetics. It is the loss of resistance to tuberculous infection which follows the development and lack of control of diabetes, which accounts for the high incidence of tuberculosis. Among the questions which have puzzled students of the disease, has been the problem whether or not the limitation in total number of calories prescribed by the physician or taken by the patient has in itself exerted a definite influence upon the development and course of pulmonary tuberculosis. It is with special reference to this question that an attempt is made to review certain features in the association of the two diseases that have come to my attention since 1920 through the analysis of 396 cases.\*

**Incidence of Tuberculosis Among Diabetic Patients in Different Countries and Different Problems of Treatment.** If the limitation of calories for diabetic patients is of significance in producing pulmonary tuberculosis, then it follows that one should be able to show differences in the incidence of pulmonary tuberculosis among the diabetic patients of this series in accordance with the differences in practice in three different periods. Thus, between 1898 and 1914 the attempt to treat diabetes mellitus was conditioned by the doctrine that, although the sugar and carbohydrate in the diet should be restricted, the amount of protein and fat consumed should be kept as high as possible in the attempt to prevent loss of weight. It was not until 1914 when undernutrition as a fundamental method of treatment in order to control diabetes was introduced that actual weighing of the food and limitation of the calories was used at the Deaconess Hospital. That period from 1914 to 1922 was a period when the calorie prescriptions were greatly restricted and, indeed, it was by no means uncommon, for patients to leave the hospital with a total dietary prescription of from 900 to 1200 or 1300 calories. Since 1922, however, although the weighing of food has continued to be prescribed, no such limitation of calories has been followed, and indeed the prescribed calories per kilogram of body weight of the patients has varied from 30 to 50 or 60 calories per kg., depending upon the age and condition of the patient.

The incidence of pulmonary tuberculosis among 3575 diabetic patients at death was as follows: from 1897 to 1914, tuberculosis caused 4.9% of 325 deaths; from June, 1914, to August, 1922, 4.9% of 835 deaths; from 1922 to 1929, 5.5% of 1434 deaths. Finally, in the late insulin era, from January 1, 1930 to 1935, tuberculosis caused 4.8% of 981 deaths. Therefore, as observed in our

\* I am fortunate in having available both the autopsy data at this hospital and the follow-up data of some 15,000 diabetic patients from 1898, when Dr. Joslin began practice.

series, there was no significant variation in the percentage of deaths from pulmonary tuberculosis during the period of maximum treatment with undernutrition.

A better method of analysis is an expression of the death rate from tuberculosis in relation to the total years of diabetic life, as shown in the following table:\*

YEARS OF LIFE EXPOSED, TUBERCULOSIS DEATHS AND DEATH RATES IN SPECIFIED PERIODS.

	Years exposed	Expected tuberculosis deaths	Tuberculosis death rate per 1,000
1897 to 1913 . . . . .	1,551	17	11.0
1914 to August 6, 1922 . . . . .	5,368	61	11.3
August 7, 1922 to 1928 . . . . .	18,027	74	4.1

The decrease in tuberculosis during the insulin era from a rate of 11.3 to 4.1 is clearly evident.

In the period 1898 to June, 1914, the average duration of diabetes to death was 4.8 years of 331 fatal cases in a total of 1588 years of diabetes. Of these cases, 19 died of tuberculosis, or 1 case per 83.6 years of diabetic life. Between June, 1914, and August 1, 1922, the average duration of diabetes to death was 6 years for 597 cases, a total of 3582 years of diabetic life, and there were 47 cases of tuberculosis (1 case in 76 years of diabetic life). Between 1922 and 1930, among 1401 fatal cases with total years of 11,441.2 of diabetic life, there were 87 cases of tuberculosis. Thus, the incidence has fallen to 1 case in 131 years of diabetic life. In the first two periods, then, characterized first by overfeeding and then by underfeeding approximately the same incidence of tuberculosis occurred. Improvement in the rate occurred during the last period when better control of the diabetes was brought about, chiefly through the use of insulin. Indeed, we may expect still further surprises in our tuberculosis statistics. In the last 3 years (ending Jan. 1, 1940) no case has occurred in a diabetic under 20 years of age.

Furthermore, if we can compare the incidence of pulmonary tuberculosis in American clinics exemplified by this hospital, with the incidence among diabetic patients whose later course has been carefully followed up in the European centers, quite a different picture is presented. In Labbè's<sup>7</sup> large hospital clinic in Paris, pulmonary tuberculosis caused 40% of the deaths in 1930, 1931 and 1932. Ponteva<sup>4</sup> reports a follow-up of 86 patients with diabetes treated before insulin and 645 patients treated since the introduction of insulin in Finland; pulmonary tuberculosis caused 18.8% of the total deaths in their follow-up. Bertram,<sup>1</sup> in Hamburg, reported that 80% of his cases of diabetes mellitus who had had diabetic coma subsequently developed pulmonary tuberculosis. Hinnsworth,<sup>3</sup> in an analysis of 230 consecutive diabetics upon their

\* I am indebted to Mr. Herbert H. Marks of the Metropolitan Life Insurance Company for the tabulation of these data.

first hospital visit in London, found 15 cases of tuberculosis. These figures from foreign countries are cited since in each instance it is fair to state that the restriction of total calories in the diet by means of weighed diet is not carried on so rigidly as in the series used for comparison. It is evident, therefore, that the incidence of pulmonary tuberculosis among diabetic patients is much greater among patients treated with less rigid dietary control.

In our series of 396 cases, the usual etiologic factors for pulmonary tuberculosis were sought. Contact with open pulmonary tuberculosis was a necessary and prominent feature, but as you will see later, unquestionably nutritional and constitutional factors are of great importance.

Unfortunately, pathologic data bearing on our problem are conspicuously few. At this hospital we have only had 17 autopsies performed upon tuberculous patients in about 360 autopsies. The descriptions of the findings in autopsies upon diabetic patients with tuberculosis in the literature are in most instances not very detailed. Nevertheless, it is true that one finds in diabetic patients tuberculosis in all stages and showing no unusual tendency to caseation, cavitation or site of lesion.

**Metabolic Features Favoring Development of Tuberculosis in the Diabetic.** In this series the following facts were outstanding: 1, 83% of the cases developed active tuberculosis after the onset of diabetes. 2, Tuberculosis of adult type occurred more than 12 times as frequently in patients whose diabetes began in childhood than in Massachusetts school children followed up in State clinics. 3, Between 1923 and 1929 pulmonary tuberculosis developed in 8% of 105 diabetic patients within 3 years of recovery from coma. Among 97 patients treated for coma between February, 1929, and November, 1932, 24 died of other causes within a year or two. Of the 73 remaining patients, 13 have developed tuberculosis within 5 years. So far as I know, no other metabolic disorder or no other clinical condition can be predicted to result in pulmonary tuberculosis in almost 20% of the cases within 5 years. Considering the subject from the other angle, when we reviewed the 396 cases, almost 20% were known to have had diabetic coma before we saw them or at some other hospital or under family physicians at home. Although we cannot get reliable data for the entire series and particularly for the entire period, it is very likely from an analysis of the course and symptoms that the incidence of severe acidosis, even though it did not reach the stage of full coma, was probably close to 50% in this series. The existence of coma does not necessarily mean that the diabetes is fundamentally severe diabetes. In fact, quite the reverse is often the case. A young woman who required 1100 units of insulin in 11 hours to bring her blood sugar from 1100 to 200 mg. per 100 cc. recovered from her coma, in which she had been anuric and pulseless, finally left the hospital with such mild diabetes that she did not need insulin at all. The existence

of coma is primarily evidence of gross lack of control and overconsumption of the patient's stores of food by reason of complications such as fever or infection. 4, Great loss of weight has been a striking feature of the patients. Actually, however, when we come to analyze this series, this fact may not be used as an argument in support of the idea that the prescription of limited calories was of itself an etiologic factor. Somewhat to my surprise, I found that in those patients who had lost from 30 to 50 pounds in weight (and actually in 219 cases the average loss of weight was 42 pounds, and loss of weight in excess of 75 pounds occurred in 19 cases) that these losses of weight occurred during periods when the diabetes had been uncontrolled. That is, the losses of weight occurred during those first months or first years of the diabetes, when in many instances the diabetes was not even discovered and when the patient, to use his own statement, was "eating his head off."

For an understanding of the effects of these metabolic disturbances we may turn to the conditions possibly favoring the growth of the tubercle bacillus.

**Lipid Content of Diabetic Lungs.** One of the most characteristic features of diabetic tissues is the remarkable alteration of the fat content of certain organs, namely, the liver, spleen, arteries and nerve tissues. In cases of the most advanced disturbance of diabetic metabolisms, as occurs in diabetic coma, particularly if the patient has been emaciated, there is marked infiltration and increase in the fatty content of the liver and frequently there is an increase in the fat content of the blood. Unfortunately, there are not many figures available for comparison either in human beings or in animals. In human lungs, Root and Bloor<sup>6</sup> found phospholipid values of 0.94 and 0.89 and cholesterol values of 0.24 and 0.31 in non-diabetic lungs. Nevertheless, in 26 diabetic patients analyzed, some striking differences were found. Twelve cases had a phospholipid value exceeding 1.1 gm. per 100 cc. Only 3 of these cases were diabetics of short duration. One who died in coma had an area of healed tuberculosis in one apex. Another woman had healed tuberculosis and a fatty liver. Actually, 5 out of these 12 patients showed evidence of healed or healing tuberculosis at an apex. These fat-filled livers were present in 4 cases and in 5 there was lipoidosis of the spleen. Cholesterol values also showed some variation from normal. One interesting feature was a low phospholipid value in certain cases and this must be considered together with the low phosphorus content of diabetic cataracts, described from this hospital laboratory by Carey, Hunt, Waite and Beetham.<sup>2</sup> Since we know that the phosphorus metabolism is clearly linked with the carbohydrate metabolism, this may provide a clue which should be followed up.

**Control of Diabetes by Insulin and Diet.** The control of the diabetes as indicated by maintenance of normal weight, strength, avoidance of acidosis, excessive hyperglycemia and glycosuria is essential.



The use of insulin should never be omitted in any diabetic patient, particularly in early life or in middle life, if tuberculosis has ever been present or indeed, if known contact with an active, positive sputum case has been present. One-half of the patients treated at this hospital receive in the morning before breakfast a small dose of crystalline insulin combined with a dose of protamine zinc insulin. A practical advantage of protamine insulin in treating tuberculosis is its reduction of the frequency of injection. The fundamental advantage of protamine zinc insulin is the more regular control of the diabetes which is possible, especially when it is combined with a small dose of crystalline insulin. The action of crystalline insulin—as at present manufactured—is only a little more prolonged than that of regular insulin. However, it is a more pure product. Insulin reactions do occur in tuberculous patients with possibly greater ease than in non-tuberculous patients, particularly if the tuberculosis is far advanced, or if the patient is emaciated and, of course, if there has been an involvement by tuberculosis of the liver or adrenals with a destruction of their opposing function. The striking feature about patients with tuberculosis after a period of adjustment in the hospital, it is true, is that the amount of insulin required in cases with positive sputum has really been no greater than the amount required by patients of similar age without complications.

The diet of diabetic patients in general, but especially the diabetic patients with tuberculosis, should be superior in every respect to the average diet. I mean by this that every bit of modern knowledge of dietary objectives, not only with regard to the calories but with regard to the minerals and vitamins present in the diet should be utilized. The object of treatment should not be dictated solely by a regard for sugar-free urine and normal blood sugar, if that leads to a diet too poor in carbohydrate or too low in calories or to the use of unnecessarily large doses of insulin, which may provoke an overactivity of the counterregulatory and opposing influences in the organs. Glycogen impoverishment favors acidosis either of mild or threatening type, which in turn is most unfavorable to improving the resistance of the patient and, on the other hand, of itself it may prepare the way for serious hypoglycemia. Richardson's<sup>5</sup> experiments with depancreatized animals again indicate the value of liberal glycogen deposits in liver and skin in relation to infection. The use of a diet excessively high in fat, in patients who are emaciated or cachectic, may lead to such an increase of cholesterol in the blood as will favor vascular disease. Low values for cholesterol of the blood are usually accompanied by a special tendency to grave insulin reactions. We see no reason to believe that pulmonary hemorrhages are in any way due to insulin or produced by it. They are more likely due to overactivity of the opposing mechanisms with the outpouring of adrenalin, increased tone in the vessels and increase in blood pressure. In general, diets

of diabetic patients with tuberculosis should have from 150 to 225 gm. of carbohydrate and from 70 to 140 gm. of fat. A standard diet may be said to include approximately 150 gm. of carbohydrate, 80 gm. of protein, 100 gm. of fat, or a total of 2100 calories. A diet to increase weight might include 250 gm. of carbohydrate, 87 gm. of protein, 110 to 120 gm. of fat.

**Case Abstract.** As an example of our present dietary plan, I will cite the case of a young student, aged 18 years, at the onset of diabetes in September, 1926. His weight at that time was 110 pounds net and indeed he had never weighed any more. His father was of similar slender build. The diet prescribed at that time included 140 gm. of carbohydrate, 70 gm. of protein and 118 gm. of fat. In May, 1937, there was a small area of opacity observed in the fifth interspace posteriorly in the outer half of the chest about the size of a 25-cent piece. He spent some months at the state tuberculosis sanatorium and upon return this area had been replaced by a smaller area, somewhat more dense and the process seemed quiet. He had no fever and no cough. His weight remained unchanged. In the spring of 1939 Roentgen rays again showed a slight increase in the soft haziness at this area and again he spent several months in a sanatorium and was discharged arrested.

His present diet consists of carbohydrate 160 gm., protein 81 gm. and fat 116 gm.; total calories of 2016. His weight is 110 pounds and he is taking 7 units of crystalline insulin and 18 units of protamine insulin.

TABLE 1.—MINERAL AND VITAMIN VALUES IN DIET FOR CASE 6532, AGED 18 YEARS AT ONSET OF DIABETES IN 1927. PULMONARY TUBERCULOSIS DEVELOPED MAY, 1937. WEIGHT 110 POUNDS NET.

(Carbohydrate 160 gm., protein 80 gm., fat 116 gm., calories, 2016, crystalline insulin 7 units, protamine zinc insulin 18 units.)

Foods.	Amount, gm.	Ca, gm.	P, gm.	F, gm.	Vitamin A precursor carotene, I.U.	Vitamin B <sub>1</sub> (thiamin), I.U.	Vitamin C (ascorbic acid), I.U.	Vitamin D (irradiated ergosterol), I. U.	Vitamin B <sub>2</sub> (riboflavin), micrograms.	Nicotinic acid (pellagra preventive factor).
Milk . . .	240	0.29	0.21	0.58	240	24	..	4.8	0.48	Fair
20% cream. .	120	0.12	0.21	0.48	1250	..	..	12.0	..	..
Oatmeal . . .	15	0.01	0.05	0.5	..	15	0	..	3.0	None
Orange . . .	425	0.13	0.08	1.02	212	..	2000	..	33.0	Slight
Egg (1) . . .	..	0.04	0.09	1.26	357	13	0	50	250.0	Fair
Bacon . . .	15	..	0.03	0.02	0	26	..	..	..	..
Butter . . .	50	0.01	0.01	0.10	750	..	..	50	..	Slight
Bread (dark) .	70	0.04	0.13	1.12	0	42	..	..	..	None
Meat . . .	150	0.015	0.30	6.2	72	37	..	..	..	Good
Potato . . .	180	0.02	0.11	1.53	54	36	270	..	17.0	None
5% vegetable .	150	0.10	0.10	3.8	26790	45	1200	..	85.0	Fair
10% vegetable	180	0.10	0.09	1.04	5900	45	126	..	36.0	Slight
Cod-liver oil .	5	..	..	..	10000	0	..	500.0	..	None
Totals . . .	..	0.88	1.41	17.65	45625	283	3596	616.8	424.48	

NOTE: Whole-wheat or dark bread, spinach and lettuce among vegetables, are recommended and here calculated. Liver at least once a week.

If we run over the composition of this diet for essential mineral and vitamin values, we may begin with the calcium. Calcium content of the diet has special importance in diabetes since in diabetic patients with acidosis or diarrhea, both of which are common, there is a negative balance of calcium. It is by no means rare to have a thinning of the bones generally, so that in diabetic patients we have not only frequent fractures but sometimes spontaneous fractures, particularly of the spine in older patients. This patient's diet, then, containing milk and cream with a good deal of fruit juices, provides a total of 0.88 gm. of calcium, which is a normal figure. Phosphorus content is 1.4 gm., again normal; with iron there is a special relation again to diabetes in two ways. In the first place, hemochromatosis (or bronze diabetes) is by no means rare and this appears to be in some way a disorder of the iron metabolism. Secondly, anemia develops with greater ease in diabetic patients, particularly in the presence of complications and it is usually of the iron-deficiency type. This diet provides 17.6 mg. The vitamin A requirement, as shown on the cards which I have passed around, is more than 6000 I. U. The vitamin B<sub>1</sub> or thiamin is especially important in relation to diabetic neuritis and in this case the requirement of 200 units is well met. Vitamin C, vitamin D, vitamin B<sub>2</sub>, riboflavin and nicotine acid are present in the amounts shown.

In order, however, to obtain a diet that is adequate one must remember certain simple requirements. In the first place, dark bread or whole cereals must be used. Vegetables rich in iron, including spinach and lettuce, are essential and liver should be included. Most of our diabetic patients should take some cod-liver oil at least during the winter months.

**Summary.** 1. In a review of the possible etiologic factors in 396 cases of pulmonary tuberculosis in diabetic patients, limitation in calories appeared to have less influence than lack of control of the diabetes.

2. Acidosis or coma preceded the development of tuberculosis in at least 20% and probably nearly 50% of the cases.

3. The use of insulin and diets adequate not only in the balance of carbohydrate, protein and fat, but in their content of vitamins and minerals is emphasized.

4. The tuberculosis death rate among diabetics per 1000 fell from 11 prior to the use of insulin to 4.1 during the first 6 years after the use of insulin.

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## GASTROSCOPIC FINDINGS IN PATIENTS WITH DUODENAL ULCER.

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*"Klinische Gastritisforschung ohne Gastroskopie ist nicht mehr möglich"*—  
(KATSCH: Handb. d. inn. Med., 1, 455, 1938).

As is well known, there is a good deal of disagreement between the gastroscopic and the pathologic-anatomic conceptions of the pathogenesis of peptic ulcer.

Konjetzny<sup>4</sup> and those who agree with him claim that chronic ulcer is the end product of a primary chronic gastro-duodenitis that passes through the catarrhal stage and then the erosive stage, reaching its climax in the ulcerative stage with the formation of one or more chronic ulcers.

In contrast to this view, Schindler<sup>5</sup> and other gastroscopists look upon chronic peptic ulcer and gastritis as two different lesions without causal connection, and think that gastroscopy in most cases of chronic ulcer will not reveal any gastritis. Gastritic changes may appear only in cases where the ulcer gives rise to retention of the stomach contents; these changes are secondary and curable. In primary gastritis, it is true, ulcerations may appear; but they do not develop into chronic ulcers, as they are acute and transitory phenomena.

Pathologic and clinical observations by Faber<sup>2</sup> and Konjetzny have shown that symptomatically it often is impossible to differentiate between peptic ulcer and gastritis. Torben Andersen<sup>1</sup> even goes so far as to claim that the "pyloric syndrome" is not a symptom of ulcer, but a symptom of gastritis. In resected specimens from patients who were operated for gastric or duodenal ulcer, Konjetzny,<sup>4</sup> Faber, Christiansen and Paaby<sup>3</sup> and Vimtrup<sup>6</sup> found that several presented no peptic ulcer at all but an ulcerative inflammation on both sides of the pylorus.

While the pathologic-anatomic picture of the mucous membrane in chronic ulcer includes a multitude of slight and more severe changes, the gastroscopic findings, according to Schindler, are limited at the most to a few submucous hemorrhages or solitary small erosions along the lesser curvature; and this holds good, no matter whether the ulcer is located in the duodenum or in the stomach.

The divergence between these views is so wide as to call for further study and gastroscopic investigation; and an attempt at this will be made here. In the present paper, however, the author prefers to deal exclusively with duodenal ulcer, not with gastric ulcer, partly because the duodenal is the most frequent form of ulcer, but also because the conditions here are simpler and more perspicuous.

For that purpose the author has gone through his gastroscopic material, comprising over 500 patients with organic lesions of the digestive tract, and found altogether 70 cases of roentgenologically verified duodenal ulcer, that is, patients in whom the Roentgen ray examination\* showed a constant and pronounced deformity of the duodenal cap, sometimes with a distinct notch. All cases in which the roentgenographic findings were doubtful and all cases of stenosis have been omitted. In none of these 70 cases was it practicable by relief examination to ascertain any changes in the stomach.

The patients were examined gastroscopically at a point of time when they had pronounced dyspeptic symptoms, and prior to the institution of treatment, so that an otherwise possible effect from the treatment upon the gastric mucosa can here be left out of consideration. Most of the patients were submitted to gastroscopic examination several times, a few of them up to ten times.

The present material comprises 13 women, aged from 23 to 53 years, and 57 male patients, aged from 13 to 64 years.

In 50% of the patients the lesion had persisted for more than 5 years, and most of them had gone through some form of medical treatment, or several cures in the course of time. About 20% of the patients were relatively recent cases, having had their symptoms for less than 1 year.

It will be reasonable to divide the material into groups based on the acidity of the gastric secretion as determined by means of the Ewald test meal, and first to consider the individual groups separately, noting whether definite gastroscopic features correspond to the different secretory groups of a clinical classification.

Such a classification of the material gives the following result:

GROUP A.	Normacidity (phenolphthalein 41-80°)	. . .	44 patients
GROUP B.	Hyperacidity (phenolphthalein 81-110°)	. . .	20 patients
GROUP C.	Hypacidity (phenolphthalein < 40°)	. . .	3 patients
GROUP D.	Anacidity (histamine-refractory achylia)	. . .	3 patients

Total	. . . . .	70 patients
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GROUP A. *Normacidity.* Of the 44 patients belonging to this group, 13 presented normal gastroscopic features, while it was possible in the remaining 31 patients to demonstrate more or less pronounced changes in the mucous membrane. In 19 patients these changes were those of a chronic superficial gastritis, and 6 patients showed features of chronic hypertrophic gastritis, while evidence of a beginning chronic atrophic gastritis ("patchy atrophy") was demonstrated in 1 patient. In 4 patients solitary erosions were demonstrated as the only gastroscopic abnormality, and 1 patient showed submucous hemorrhages along the lesser curvature in an

\* In all these cases the Roentgen ray examination was carried out by Dr. de Fine Licht, Chief of the Department of Roentgenology, to whom I am indebted for painstaking collaboration through several years.

otherwise normal stomach. The occurrence of erosions in gastritic stomachs was seen but relatively seldom, only in 3 cases. Gastroscopic reëxamination after the discontinuance of treatment showed that the observed erosions all had healed without leaving any visible marks within 2 to 5 weeks, even in cases where no improvement of the gastritis could be demonstrated after the treatment. Finally, it is to be mentioned that 5 patients with gastritis showed also submucous hemorrhages, localized as usual.

The localization of the gastritic changes is evident from the following tabulation:

Localization.	Superficial gastritis.	Hypertrophic gastritis.	Total.
Entire stomach . . . . .	5	3	8
Proximal half . . . . .	14	3	17
Antrum alone . . . . .	0	0	0

It will be noticed that in a majority of these cases (about two-thirds) the gastritis was localized exclusively to that part of the stomach which is proximal to the angulus, while in the other cases it extended over the entire stomach. An isolated affection of the antrum could not be demonstrated in any case. On the whole, it may be said that in most of the cases with gastroscopically demonstrable changes in the mucous membrane the affection consisted in the prognostically more benign superficial gastritis, while the prognostically more malignant hypertrophic gastritis was considerably less frequent; and the more severe degrees of the latter form of gastritis were not observed at all. So in this group, with normal gastric acidity, we find all three forms of gastritis represented. In other words, this group does not constitute any morphological entity.

The relation between the character of the symptoms and the gastroscopic findings is evident from the following survey:

Character of symptoms.	Gastroscopic findings.	
	Normal.	Pathological.
Pyloric syndrome . . . . .	7	18
Pyloric syndrome + vomiting . . . . .	1	4
Pyloric syndrome + hemorrhage . . . . .	0	2
Uncharacteristic symptoms . . . . .	5	7

From this it will be noticed that the typical ulcer symptoms—tardive pain, hunger pain, relief from intake of food, in some cases together with vomiting and hemorrhage—in duodenal ulcer are found far more frequently in those cases where the stomach is also affected than in cases presenting a normal stomach. On the other hand, there appears to be no particular difference in the frequency of the uncharacteristic symptoms, whether the stomach is gastroscopically normal or affected.

GROUP B.—*Hyperacidity.* Of the 20 patients belonging to this group, 5 presented a gastroscopically normal stomach, while patho-

logic conditions were demonstrated in 15, namely: chronic superficial gastritis in 13 cases, and chronic hypertrophic gastritis in only 1 case, while a solitary erosion in an otherwise normal stomach was seen in 1 case. In this group, submucous hemorrhages or atrophic changes were not observed at all.

The localization of the gastritis was as follows:

Localization.	Superficial gastritis.	Hypertrophic gastritis.	Total.
Entire stomach . . . . .	7	0	7
Proximal half . . . . .	6	1	7
Antrum alone . . . . .	0	0	0

Even though the figures are rather small, they still show that there is no recognizable difference in the character, degree and localization of the gastritis in patients with duodenal ulcer, no matter whether the values for the acid secretion are normal or increased. This means that it is not justifiable from the finding of hyperacidity in duodenal ulcer to draw any conclusions as to whether the stomach is the site of a more severe form of gastritis than is encountered in patients with normal acidity. In particular, it is unwarranted to assume a preponderance of hypertrophic erosive elements corresponding to the findings in resected specimens. Finally, like Group A, this group corroborates the view\* that antral gastritis does not occur as an affection *per se* but merely as a part of a pangastritis. Hyperacidity in duodenal ulcer does not represent a gastroscopic entity.

The relation between the character of the symptoms and the gastroscopic findings in Group B is evident from the following survey:

Character of symptoms.	Gastroscopic findings.	
	Normal.	Pathological.
Pyloric syndrome . . . . .	2	6
Pyloric syndrome + vomiting . . . . .	0	2
Pyloric syndrome + hemorrhage . . . . .	0	2
Uncharacteristic symptoms . . . . .	3	5

This is in keeping with the findings in Group A, namely: that the typical ulcer symptoms are more frequent in duodenal ulcer patients with a gastroscopically affected stomach than in such patients with normal gastroscopic features, even though we have to be prepared among the former—duodenal ulcer patients with a gastroscopically affected stomach—to find several with quite uncharacteristic symptoms.

GROUP C.—*Hypacidity*. This group comprises only 3 patients, in whom the duration of illness was respectively 8, 6, and 3 years. Two of them had the pyloric syndrome without vomiting or hemorrhage; one had uncharacteristic dyspeptic symptoms. In the latter,

gastroscopy showed pronounced hypertrophic gastritis with erosive elements, localized to the upper two-thirds of the stomach, and most marked on the anterior wall, while the antrum appeared normal. One presented the features of a superficial pangastritis. In one the entire stomach looked normal.

GROUP D.—*Anacidity*. The 3 patients belonging to this group had had symptoms for respectively 1, 10, and 20 years. Two of them had a typical pyloric syndrome; the third had uncharacteristic dyspeptic symptoms. In the last 2 patients the stomach appeared normal, in the first there was a superficial pangastritis without erosions or hemorrhages. No atrophic area was seen in any of these cases.

The last two groups further illustrate the significance of gastroscopy to the clinical diagnosis of diseases of the stomach; and, like Groups A and B, they show that in patients with duodenal ulcer neither the clinical symptoms, nor the values for acidity, nor the Roentgen ray relief are serviceable criteria as to the state of the stomach.

**Discussion.** Considering the findings in these examinations as a whole, regardless of the secretory conditions, it turns out that in the 70 patients with duodenal ulcer it was practicable gastroscopically to demonstrate definite changes in the mucous membrane of the stomach in 49 cases (70%) while the gastroscopic findings were normal in 21 patients (30%).

The character and frequency of the various gastric findings are recorded in the following survey:

Gastritis, chronic superficial . . . . .	34 patients
Gastritis, chronic hypertrophic . . . . .	8 patients
Gastritis, atrophic . . . . .	1 patient
Erosion in normal stomach . . . . .	5 patients
Erosion in abnormal stomach . . . . .	3 patients
Submucous hemorrhages in normal stomach . . . . .	1 patient
Submucous hemorrhages in abnormal stomach . . . . .	5 patients

So, in contrast to the view of Schindler, the gastroscopic findings show that the stomach in a majority of these cases was the site of pronounced pathologic changes. The most frequent finding was benign superficial gastritis, a form of gastritis that is curable. According to Schindler, in about 2% of the cases it subsequently turns into atrophic gastritis, a condition which in the present material was found in 1 patient. The next in frequency was the more serious and incurable hypertrophic gastritis. Solitary erosions occurred in several cases as the only pathologic finding as well as a gastritic phenomenon. The same applies to the submucous hemorrhages. In 17 patients the gastritic changes were distributed diffusely over the entire stomach, whereas in 25 patients they were localized exclusively to the proximal part of the stomach, corroborating the



view expressed by Schindler that antral gastritis does not exist as an affection *per se* but merely as part of a pangastritis.

The demonstrated frequency of gastritis in duodenal ulcer cannot be taken to confirm the findings of Konjetzny, however, as there is a considerable difference, qualitative as well as quantitative, between the changes here observed and those found in the resected specimens. Of course the objection may be raised, that gastroscopy can give information merely about the surface of the gastric mucosa, not about the deeper changes. But it must be kept in mind that the divergence does not concern microscopic findings, but, on the contrary, massive inflammatory changes in all the layers of the mucous membrane, which in resected specimens are visible also macroscopically on the mucosal surface where erosive, ulcerative and productive processes are found side by side. It has to be maintained that such severe changes cannot be overlooked by an experienced gastroscopist. In the present material, there is only one case where the gastroscopic picture of the mucosa corresponds to that which Konjetzny considers paradigmatic—namely, in a patient belonging to the hypoehylic group who presented an erosive hypertrophic gastritis. If resection had been performed on this patient, however, the resected specimen would not have presented the picture Konjetzny emphasizes as typical, for here the gastritis was localized exclusively to the proximal part of the stomach.

Even though the findings here reported thus confirm only to a limited extent the features which Konjetzny and those who agree with him look upon as the general pathologic-anatomic finding, there can be no doubt that a gastroscopic picture corresponding exactly to this finding may be encountered in some cases. In such cases, then, the gastroscopic and the pathologic-anatomic findings may be quite in harmony morphologically. On the other hand, it will be difficult gastroscopically to find evidence in support of the conclusions Konjetzny and others have drawn concerning the etiology and pathogenetic relationship between gastritis and chronic peptic ulcer, conclusions that once threatened to make resection of the stomach a standard therapeutic method.

To illustrate this point it will be appropriate to cite the case history of a patient not included in the material here concerned.

**Case Report.** An English scientist, 60 years old, for the last 3 years had been troubled by typical ulcer symptoms that were gradually getting worse during the last 6 months, and on which account he entered the hospital (Reg. No. Dep. B, 590/39). On admission, his general condition appeared to be fairly good. Hemoglobin: 107%. Blood urea: 32 mg. per 100 cc. Urine: No albumin or sugar; ++ chloride. Shortly after admission he commenced having copious watery vomiting, up to 500 cc. at a time. In connection herewith, azotemia appeared, with increase in blood urea to 72 mg. per 100 cc. and achloruria. As administration of vagospasmyl gave no improvement, treatment was instituted with daily gastric lavage and depositing of saline in the stomach. The azotemia yielded rapidly to this

treatment, but the pain persisted. Roentgen ray examination, one week after admission: Stomach filled with food remnants and fluid; pronounced gastrectasis with 24 hours' retention. Roentgenological diagnosis: Pyloric stenosis. Roentgen ray examination repeated one week later: Same findings as before.

*Gastroscopy*, 3 weeks after admission: Very marked gastric changes throughout the stomach, but more pronounced superiorly on the posterior wall and along the greater curvature. Intense redness and succulence of the folds, which are thick, tortuous and studded with erosions. Between the folds, firmly adherent muco-pus. Angulus thick, dark red in color, glossy, eroded. The changes continue out in the canal. Through the pylorus, bile-colored duodenal juice squirts into the stomach. Gastroscopic diagnosis: Erosive pangastritis, severe degree.

After these findings further medical treatment seemed to offer only a poor outlook, and the advisability of an operation was considered. Under continued gastric lavage, however, the vomiting ceased, the pain subsided, and the patient gradually became able to tolerate a fever diet.

Roentgen ray examination after 3 weeks' continued gastric lavage showed: Relief more conspicuous. After filling, the stomach is large and atonic, yet far smaller than before. The emptying proceeds more lively, so that the duodenum fills better. The duodenal cap is constantly deformed, with eccentric location of the pyloric inlet and considerable dilatation of the lateral recess, possibly a notch, so that there can be no doubt about the presence of a duodenal ulcer. Four hours after intake of the contrast meal the stomach has emptied completely.

After these roentgenographic findings and the marked improvement in the condition of the patient, there was no longer any reason to consider surgical treatment.

*Gastroscopy*, 16 days after the first examination: The pyloric part, the antrum and the lower half of the stomach are perfectly normal as to color, juiciness and structure. No erosion is seen, nor mucus between the folds. Superiorly, below the cardiac orifice there are still some remnants of the gastritis as redness, succulence and increased vulnerability. Inferiorly, toward the greater curvature, there is a single pea-sized erosion on the anterior wall.

Next day the patient was discharged from the hospital, free from symptoms.

This case is instructive, and it possibly can give an explanation of the divergence between Konjetzny and Schindler. There can hardly be any doubt that if resection had been performed on this patient, as was at one time considered when his illness was at its worst, the resected specimen would have presented macroscopically as well as microscopically the very picture on which Konjetzny and his followers base their theories. There would have been a duodenal ulcer together with a violent, erosive, antral gastritis. The course of the disease showed, however, that these pronounced changes were of an acute character, healing within a few weeks, when the pyloric spasm subsided and the retention disappeared.

To those who have had the opportunity gastroscopically to follow such a case—which is by no means unique—the question suggests itself, whether the changes found in the resected specimens really are not to be looked upon as being of a similar nature as the ones observed in this patient. The whole course of the disease as re-

corded here, with an almost miraculous improvement of the clinical symptoms running parallel with a rapid healing of very severe changes in the stomach, while the roentgenographic changes in the duodenum remained constant, may hardly be interpreted otherwise than indicating that the duodenal ulcer in this patient is the primary lesion while the gastritis is secondary. At any rate, it will be difficult from the recorded observations to find anything in support of the contrary view.

**Summary and Conclusions.** 1. It may be taken as the general rule that patients with a non-stenotic duodenal ulcer are liable to pathologic changes in the gastric mucosa, even though no abnormality may be demonstrated by roentgenography or Ewald test meal.

2. Deviations from normal acidity furnish no basis for conclusions about the character of these changes or their location in the stomach.

3. To settle the question about the state of the stomach gastroscopy is the method of examination.

4. The gastric changes include all three forms of gastritis, the preponderant being the relatively more benign chronic superficial gastritis, which in some cases possibly may go on to atrophy. Chronic hypertrophic gastritis is more serious but less frequent. Solitary erosions and hemorrhages may make their appearance as elements of a gastritis or as the only gastroscopic abnormalities. The same applies to the punctate submucous hemorrhages.

5. The gastritis may be total or partial; in the latter case, it is localized to the fundus of the stomach. If the antrum is involved, it is always as part of a pangastritis, whereas an isolated antral gastritis is not seen gastroscopically.

6. The erosions are acute manifestations that may heal in a few days, no matter whether or not the gastritis improves at the same time. Transition to a chronic gastric ulcer has not been observed.

7. The typical ulcer symptoms seem preferably to make their appearance in cases where the stomach is also affected.

8. Acute gastric retention may be associated with severe erosive changes in the stomach corresponding to the findings in resected specimens. These changes are inconstant and may disappear rapidly when the retention subsides. Probably this condition does not involve a primary gastritis, as has been claimed by Konjetzny, but more likely secondary peptic injury, as asserted by Schindler.

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## INVERTED DUODENUM.

### ITS CLINICAL SIGNIFICANCE WITH REPORT OF 14 CASES.

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IN recent years there has been considerable interest shown in diseases and anomalies of the duodenum. In this communication an anomalous condition in the form of an inverted duodenum is presented with a report of 14 cases. Anomalies of the first portion of the duodenum are very rare, since it arises from the foregut. Most anomalies of the intestine arise from errors of rotation of the midgut. Inverted duodenum is a congenital anomaly due to a developmental error involving the caudad segments of the duodenum. The condition is not common, but occurs more often than a survey of the literature would indicate. Bryce<sup>2</sup> and others consider it a rare anomaly.

The true incidence of this anomaly has not been determined as far as one can ascertain from the literature. The roentgenologic incidence of inverted duodenum is extremely low. In approximately 20,000 gastro-intestinal Roentgen studies 14 instances (0.07%) have been observed. Anderson<sup>1</sup> noted the condition to occur once in the examination of 100 consecutive subjects in the dissecting room. The incidence of 1% in his study seems to be rather high. The total number of reported cases has not been tabulated. Sandera<sup>4</sup> reported 10 cases, 2 of which were confirmed by operation. Weinbren and McGregor<sup>5</sup> reported 11 cases, and Hurthle<sup>3</sup> 5 cases.

This anomaly has been described as a form of mobile duodenum to which Sandera gave the term of "duodenal dystrophy." Duodenum inversum is described as a transitional type of mobile duodenum, but he believes that it is not a true form of mobile duodenum. The fact that the various groups of mobile duodenum are not sharply defined probably accounts for its description under various headings. There has been a tendency in recent years to segregate the different forms of duodenal abnormalities into definite entities. Sandera deserves credit for pointing out and giving a full description of the varieties of mobile duodenal abnormalities.

The association of other congenital anomalies coexisting with inverted duodenum should be emphasized. However, in our series of 14 cases, which do not include those with non-rotation of the intestines, there were no other gastro-intestinal anomalies that could be recognized by means of the Roentgen examination. In cases of

inverted duodenum, evidences of defective mesenteric attachment have been observed. There may be changes in position and shape of the head of the pancreas, and other pancreatic anomalies.

The condition may be found at any age. In our 14 cases the ages ranged from 26 to 67 years (average, 47 years); in Weinbren and McGregor's 11 cases, from 26 to 70 years. The average age in Sandera's 10 cases fell in the third decade. The condition predominates in the male sex. In our series, there were 11 males and 3 females. In Weinbren and McGregor's 11 cases, 7 were males and 4 females.

Clinically, this anomaly presents no characteristic symptoms or signs which might aid in the diagnosis. It is probable that this condition often exists without giving rise to any symptoms whatever, and, on the other hand, many of the symptoms may arise from an associated lesion or complication. Epigastric pain or discomfort, nausea, belching and gaseous distention are the most prominent symptoms encountered in this condition. However, jaundice and diarrhea are not uncommon. Table 1 presents the pertinent symptoms and associated conditions observed in our 14 cases. When stasis occurs as a result of this anomaly a certain train of symptoms may appear depending upon the degree of stasis. Among these may be mentioned loss of appetite, nausea, epigastric discomfort, vomiting and headaches, often of the migraine type. In some, so-called bilious attacks may occur at varying intervals, usually preceded by periods of constipation. When these attacks are frequent, loss of weight and strength supervene and in certain individuals neurasthenic symptoms become a prominent part of the picture.

In our 14 cases the symptoms varied, and seemed to be due to the associated or complicated conditions. Symptoms of peptic ulceration were most common, but only 5 of our cases presented roentgenologic signs of peptic ulceration. According to Sandera, symptoms are due to the hindering of the passage of the duodenal contents. He found that nearly all of his patients complained of abdominal pain, discomfort after eating and spells of fulness and nausea. It has been pointed out that this condition may predispose to pancreatitis and cholecystitis as a result of secondary involvement through the ducts. Ordinarily, however, these complications do not occur unless there is an anomalous development, change of position or twist of the bile duct in consequence of the abnormal curve of the duodenum or they may be due to stasis in the duodenum causing a back-flow through the ducts into the pancreas or gall bladder.

The following brief abstract of one of our cases illustrates some of the clinical aspects of an inverted duodenum case associated with a mild cholecystitis.

Mrs. R. W. B., aged 55, complained of belching, nausea, regurgitation of bile, loss of appetite, vague abdominal pains and loss of weight over a period of 5 years. Recently she had noticed evidence of jaundice. Physical

TABLE 1.—SUMMARY OF CLINICAL DATA IN 14 CASES OF INVERTED DUODENUM.

Cases.		Sex.	Age.	Pain.	Appetite.	Constipation.	Vomiting.	Gas belching.	Nausea.	Loss of weight.	Jaundice.	Headache.	Test meal.		Associated conditions.
													Free HCl.	Total.	
1	H. L.	M	57	+	Poor	+	+			+			0	18	Carcinoma of stomach.
2	F. S.	F	42	+	Poor	+		+				+	57	78	Gall stones, duodenal diverticulum and stasis.
3	S. J. S.	M	61	+		+				+					Mediastinal neoplasm.
4	F. L.	M	54		No	gastro-	intest	inal sympto		ms.			56	82	Pulmonary tuberculosis.
5	F. W. V.	F	45	+	Poor								39	58	
6	F. S. J.	M	28	+	Poor	+		+							
7	J. B.	M	67	+									36	54	Gastric ulcer; pyloric obstruction.
8	H. K. D.	M	40	+	Poor								38	56	Peptic ulcer.
9	J. T.	M	54	+		+									
10	A. M.	M	26	+	Good								50	58	
11	C. H. B.	M	38	+			+			+					Gastric ulcer.
12	R. M.	M	43	+				+							Duodenal ulcer.
13	M. P.	M	44	+	Good										Duodenal ulcer.
14	R. W. B.	F	55	+	Poor			+	+	+	+		10	32	Low-grade cholecystitis.

examination was essentially negative. Urine was normal. Wassermann was negative. An Ewald test meal yielded a total acidity of 32, and free hydrochloric acid of 10. A gastro-intestinal Roentgen study revealed a normal stomach and duodenal bulb; there was an absence of the duodenal curve with a Type 2 inverted duodenum. Cholecystography revealed a gall bladder of poor density; there were no stones. Following a fat meal there was delayed emptying. A diagnosis of inverted duodenum, associated with a low-grade cholecystitis was made.

The Roentgen examination offers the only means by which a correct diagnosis can be made. A careful study of the entire course of the duodenum will clearly depict this condition. It is radiologically characterized by the anomalous position and course of the duodenum, with either shortening or lengthening of the duodenum. Several varieties of inverted duodenum may be demonstrated roentgenologically, depending upon the segment at which the developmental error occurred. The position of the duodenal bulb is never involved in this condition.

For the purpose of description we have divided this anomaly into four types. In the first a complete inversion of the entire duodenum (excepting the bulb) is observed. The entire duodenal curve is absent and its course and direction are completely changed. Instead of the descending duodenum being directed downward in the right mesial aspect, there is an elimination of the angle formed by the bulb and the second portion of the duodenum. The direction of the duodenum extends upward toward the left and backward. The third and fourth portions of the duodenum are not demarcated, cross the mid-line transversely to the left toward the duodeno-jejunal juncture. The composite picture reveals an absence of the duodenum in its normal position with complete absence of the normal duodenal C-shaped curve. In this form, the duodenum is on a higher level and is shorter than normal (Fig. 1).

In the second type, the inversion takes place in the descending arm or second portion of the duodenum at the angle with the third or transverse segment. The normal duodenal curve is again absent. The second portion appears to extend down in its normal position, or it may be pulled over to the right and upward. Instead of the

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#### LEGENDS FOR FIGS. 1 TO 3.

FIG. 1.—(Left) normal duodenal curve. (Right) Type 1 variety of inverted duodenum. Note the position of the duodenum, with complete absence of the curve. The duodenum is shortened and shows an absence of the normal demarcation of its different segments.

FIG. 2.—Two varieties of Type 2 inverted duodenum. Note the change in the direction of the duodenum which begins at the angle between the descending and transverse segments. Also note the upward direction of the ascending duodenum which occurs to the right of the descending arm.

(Left) duodenum crossing the midline behind the duodenal bulb.

(Right) duodenum crossing the midline behind the duodenal bulb.

FIG. 3.—(Left) Type 3 inverted duodenum, presenting a redundancy of the superior duodenum, with lengthening of the duodenum.

(Right) Type 4 inverted duodenum illustrates a complete inversion of the duodenum in a case of congenital non-rotation of the intestine.

1



2

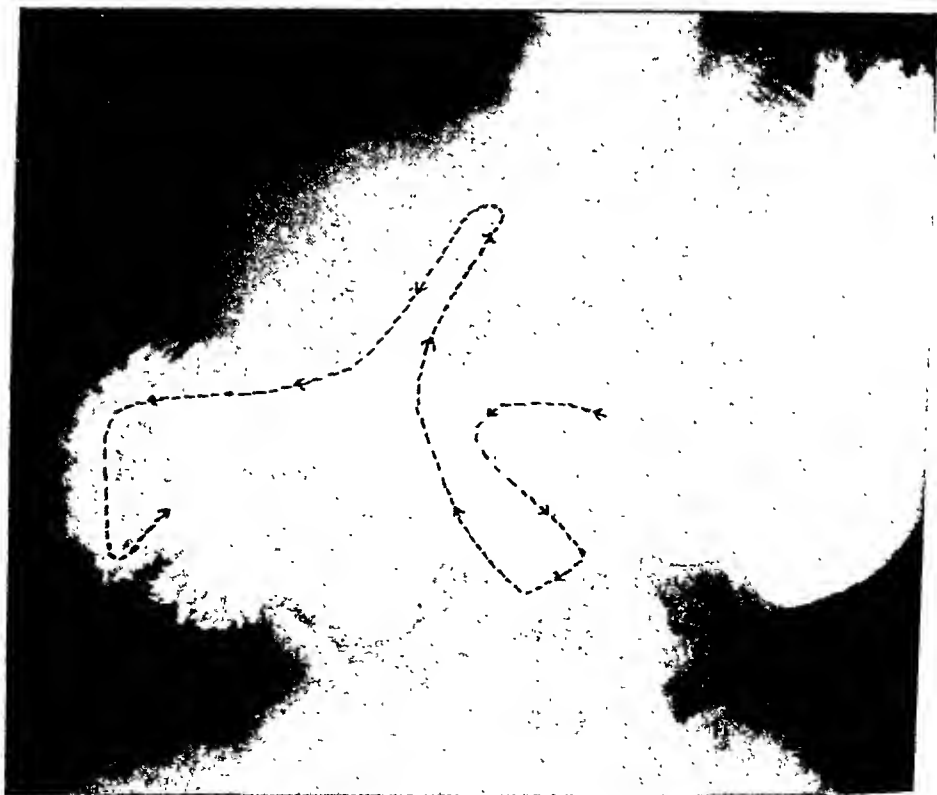


3





4



third portion crossing transversely toward the left, this segment makes a sharp upward and outward turn towards the right side, and then ascends to the right of the descending arm, crossing behind or over the duodenal bulb. The duodenum is apparently of normal length (Figs. 2 and 4).

The third type reveals a lengthening of the duodenum, an absence of the normal duodenal curve and marked redundancy of the superior duodenum. The course of the duodenum is similar to that of the second variety, except that in this form there is a lengthening of the duodenum with a sagging loop. The position of the duodenum is displaced to the right. The duodeno-jejunal juncture may also be displaced mesially (Fig. 3).

In the fourth type, there is not only an inversion of the duodenum but in addition a congenital non-rotation of the intestine, with the entire duodenum situated on the right side of the abdomen. In this form there is an absence of the duodeno-jejunal angle; the duodenum joins the jejunum on the right side of the abdomen (Figs. 3 and 5).

It must be pointed out that the duodeno-jejunal angle may be abnormally situated. The position of the stomach may be directed further to the left than normal. The position of the stomach in our 14 cases was normal. Weinbren and McGregor noted that the stomach may be further to the left of the spinal column than usual. In the true form of inverted duodenum the position of the duodenal bulb is relatively normal and does not appear to be involved in the anomalous position of the remaining duodenum. Our studies did not reveal any change in the position of the duodenal bulb. Occasionally it may be directed transversely.

Changes in the motility of the duodenum are often observed. In the first type, it usually empties rapidly, while in Types 2 and 3 it may be retarded, especially in the latter variety, where varying degrees of stasis with dilatation of the lumen may be observed. In the cases presenting duodenal stasis there may be secondary involvement of the pancreatic, biliary and hepatic structures. In the redundant variety, there is nearly always a stasis with disturbance of motility of the superior duodenum. In the fourth type, with non-rotation of the intestine, duodenal motility is generally accelerated.

The stomach ordinarily empties normally in most instances. In our 14 cases there was no delay in emptying. Sandera and Hurthle likewise found no delay in the emptying time of the stomach. However, Weinbren and McGregor observed a slowing of the emptying rate in 3 of his 11 cases.

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#### LEGENDS FOR FIGS. 4 AND 5.

FIG. 4.—A typical case of inverted duodenum, with complete absence of the duodenal curve. Note direction of the duodenum at arrows.

FIG. 5.—Inversion of the duodenum in a case of partial non-rotation of the intestine. Note the absence of the normal duodenal curve and change of position of the duodeno-jejunal flexure from the left side to the right.

In the Roentgen examination of the duodenum care must be taken to obtain a full and clear view of the entire duodenal curve. Fluoroscopic examination is most important in portraying this anomaly. Prone, supine, lateral and oblique views are often required completely to visualize the whole course of the duodenum. Even with the above positions the distal portion of the duodenum may be overshadowed by the stomach so that the complete curve and course are obscured. A duodenogram, in which the opaque meal is placed directly into the duodenum through a tube, is an ideal procedure to bring out the whole course of the duodenum, of which it gives a clear unobscured view.

In the treatment of this condition conservative medical management is usually sufficient to bring about symptomatic relief, especially since in the majority of these cases periods of well-being are quite characteristic. In those cases in which the associated lesion is responsible for the clinical manifestations, treatment necessarily is directed towards overcoming the underlying disease. To accomplish this, it might occasionally be advisable to conduct a rest cure in bed, preferably in a hospital, for from 4 to 6 weeks, during which time general upbuilding measures might be instituted in addition to the therapy of the underlying condition. When duodenal stasis is marked, transduodenal lavage with magnesium sulphate or Ringer's solution is usually very beneficial. The diet should be of the bland type and of a high caloric and vitamin content. When adequate medical management fails to bring about relief, surgical intervention may become necessary. The type of operation performed will depend not only upon the patient's condition but also on the lesions discovered after a thorough exploration.

**Summary.** Anomalies of the duodenum are far more common than is indicated by a survey of the literature. Of these, the inverted duodenum is of considerable interest. Fourteen cases are here recorded. Since the roentgenologic incidence of this condition occurs in only 0.07% of cases, it was considered of general interest to report this series. A detailed radiologic description of the anomaly is given, together with an anatomic classification. Clinically, there is no characteristic symptomatology, the picture being often that of a complication or an associated lesion. Many instances undoubtedly occur without presenting any symptoms whatever. The diagnosis must be based on a thorough Roentgen-ray investigation. These cases deserve careful study not only from an anatomic standpoint but also from the clinical aspect, since their early recognition and effective treatment may prevent the occurrence of secondary conditions such as cholecystitis and pancreatitis.

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## THE USE OF SULFAPYRIDINE IN STREPTOCOCCUS VIRIDANS MENINGITIS.

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SULFAPYRIDINE has been used successfully in the treatment of pneumococcus pneumonia and pneumococcic meningitis,<sup>1</sup> and according to recent reports it offers hope in sub-acute bacterial endocarditis.<sup>2</sup> To date, we know of no reports on its use in meningitis due to streptococcus viridans.

Since January, 1937, we have treated 6 cases of streptococcus viridans meningitis. Two were treated with sulfapyridine and recovered; 1 with sulfanilamide, sulfapyridine, Ulcran,\* and deep Roentgen ray therapy, and recovered; 3 were treated with sulfanilamide and failed to improve.

**Case Abstracts.** CASE 1.—W. J. L., a 54-year-old negro, admitted to the Genito-urinary Service May 16, 1939, had complained for about 1 year of recurrent attacks of urinary retention relieved by passing of blood clots or catheterization, followed by hematuria.

Physical examination was negative. Cystoscopic examination revealed blood oozing from the right ureter. A retrograde pyelogram revealed numerous small stones in the left middle calyx. The upper calices on the right had a peculiar sharp configuration, and the base of the upper major calyx was quite wide, which was interpreted as possible scarring due to a calculus. Guinea pig inoculation and smears of urine were negative for acid-fast bacilli.

On the sixth day after admission he had a chill, an hour and a half later, a convulsion, and his temperature rose to 104°. Blood non-protein nitrogen taken at this time was 36 mg. per 100 cc. Within 24 hours opisthotonos was present, neck rigid, Brudzinski and Kernig's signs positive. Spinal puncture revealed turbid fluid, positive globulin, and 230 cells, predominantly polymorphonuclears. He was transferred to the Communicable Disease Service, where another spinal puncture was done and 8500 cells were found; direct smear of spinal fluid showed no organisms. He was placed on sulfanilamide and given 90 grains before the spinal fluid culture report of streptococcus viridans was received. The treatment was changed to 2 gm. of sulfapyridine every 4 hours, and the same dosage was maintained for 8 days. Two days after starting the drug the temperature returned to normal. On the third day, the spinal fluid cell count dropped to 450 and cultures were negative.

\* Ulcran (dimethyl disulfanilamide) was furnished by Winthrop Chemical Company, Inc.

The patient made an uneventful recovery, and after having been with us for 20 days was returned to the Genito-urinary Service.

## SPINAL FLUID EXAMINATIONS.

Date, 1939.	Cells.	Smear.	Culture.
5/23 . . . . .	8500	Negative	Strep. viridans
5/24 . . . . .	..	"	" "
5/25 . . . . .	..	"	" "
5/26 . . . . .	Bloody	"	" "
5/27 . . . . .	450	"	Negative
5/28 . . . . .	200	"	"
5/29 . . . . .	100	"	"
5/30 . . . . .	50	"	"
6/1 . . . . .	40	"	"
6/6 . . . . .	35	"	"

CASE 2.—J. D. W., a 22-month-old white boy, admitted to the Communicable Disease Service August 4, 1939, had been ill for 1 month with alternating periods of diarrhea and constipation. One week before admission the diarrhea became marked and slight fever developed. Two days later, fever became high (not taken), the child vomited frequently, and refused to eat. This situation persisted to the time of admission. Physical examination revealed a poorly nourished, dehydrated male child of 22 months, having frequent generalized convulsions. Rectal temperature 104.2°, pulse 96, respiration 48. The eyes rotated aimlessly; both ear drums were red; neck was rigid; Brudzinski and Kernig's signs positive.

Spinal fluid, under a pressure of 400 mm. of water, contained 1900 cells, mostly polymorphonuclears. Smear revealed Gram-positive diplococci and culture contained streptococcus viridans. Bilateral myringotomy was done on admission and for 2 days a slight serous drainage followed. Sulfapyridine was given 1 gm. every 4 hours. Spinal fluid on the day after admission contained Gram-positive cocci on direct smear, but the culture was negative. The temperature returned to normal on the 5th day. The patient was discharged on the 20th day.

## SPINAL FLUID EXAMINATIONS.

Date, 1939.	Cells.	Smear.	Culture.
8/4 . . . . .	1900	Gram-pos. cocci	Strep. viridans
8/5 . . . . .	1750	Gram-pos. cocci	Negative
8/6 . . . . .	700	No organisms	"
8/7 . . . . .	500	" "	"
8/8 . . . . .	Bloody	" "	"
8/9 . . . . .	200	" "	"
8/10 . . . . .	200	" "	"
8/11 . . . . .	Bloody	" "	"
8/14 . . . . .	100	" "	"
8/17 . . . . .	Bloody	" "	"
8/23 . . . . .	3	" "	"

CASE 3.—E. U. S., an 8-year-old white boy admitted to Communicable Disease Service September 20, 1939, had complained of headache, fever up to 103°, nausea and vomiting, pains in the legs and stiff neck of 3 days' duration. He had had pneumonia 5 months previously, and had not been well since. On admission temperature was 101.8°, pulse 120, respiration 24. His neck and back were stiff, Brudzinski and Kernig's signs positive. It was thought that there was weakness of both upper and lower extremities, although reflexes were all physiologic.

Spinal puncture revealed pressure of 150; 79 cells, 66% polymorphonuclears; no organisms on direct smear, and no growth on culture. A diag-

nosis of poliomyelitis was made, and 100 cc. of convalescent poliomyelitis serum were given. On the third day difficulty in swallowing developed, and Retan's<sup>3</sup> method of treatment was started. The next day spinal fluid cell count jumped to 1800 and the succeeding day to 12,600 with 90% neutrophils. A blood culture taken at this time produced streptococcus viridans a few days later.

Diagnosis was changed to meningitis and sulfanilamide was started. After 24 hours this was changed to sulfapyridine. Two days later spinal fluid cultures were reported positive for streptococcus viridans. Roentgen ray of sinuses and mastoids revealed no lesions and on aspiration of the sphenoid sinus no pus was found. After 5 days of sulfapyridine, no improvement was noted so sulfanilamide was started again. Cultures remaining positive, sulfapyridine again replaced sulfanilamide after 3 days. Spinal fluid cultures became negative 2 days later, but the spinal fluid cell count and general condition did not improve. Because of this, Uleran was started and deep Roentgen ray therapy was given to the base of skull. Clinical improvement was marked within 24 hours. The spinal fluid cell count dropped to 47 within 72 hours, and the temperature to normal on the fifth day. Thereafter, all medication was stopped and recovery was uneventful.

## SPINAL FLUID EXAMINATIONS.

Date, 1939.	Cells.	Smear.	Culture.
9/20 . . . . .	79	Negative	Negative
9/23 . . . . .	108	"	"
9/25 . . . . .	1800	"	"
9/26 . . . . .	12600	"	Strep. viridans
9/27 . . . . .	10000	"	" "
9/28			
9/29 . . . . .	980	Negative	Strep. viridans
9/30 . . . . .	195	"	" "
10/1 . . . . .	212	"	" "
10/2 . . . . .	1500	"	" "
10/3 . . . . .	990	"	" "
10/4 . . . . .	895	"	" "
10/5 . . . . .	1260	"	" "
10/6 . . . . .	620	"	" "
10/7 . . . . .	410	"	" "
10/8 . . . . .	500	"	No growth
10/10 . . . . .	225	"	Strep. viridans
10/12 . . . . .	840	"	No growth
10/14 . . . . .	433	"	" "
10/16 . . . . .	47	"	" "
10/20 . . . . .	10	"	" "
10/22 . . . . .	18	"	" "
10/24 . . . . .	16	"	" "
10/26 . . . . .	10	"	" "
10/28 . . . . .	10	"	" "
11/5 . . . . .	7	"	" "

**Conclusions.** While definite conclusions cannot be drawn from merely 3 cases, it would seem that sulfapyridine was responsible for the recovery of 2 of these patients and had an inhibiting effect on the organisms in the third case.

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## THE SABIN AGGLUTINATION TEST AS A CONTROL OF THE SULFAPYRIDINE TREATMENT OF PNEUMONIA.

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RECOVERY from pneumonia is believed to be dependent upon destruction of the pneumococci by phagocytes. For the phagocytes to accomplish this, however, there must be adequate type-specific antipneumococcic antibody.

In 1902 Neufeld<sup>3</sup> observed in patients recovering spontaneously from pneumonia that antibodies for the homologous pneumococcus first appeared in the blood about the time of the crisis. This was usually early in the second week of the disease in uncomplicated pneumonia. In the treatment of pneumonia with sulfapyridine, some of the first investigators noted that the marked improvement seen in the first 24 hours was deceiving. For when the drug was stopped soon after the early defervescence of fever, relapse occurred frequently, sometimes with spread to new lobes or other complications. Like many others, we had noted that when sulfapyridine was continued until the eighth or ninth day of the disease there were few relapses. As mentioned above, this corresponds with the time when antibody first appears in the blood of patients recovering from pneumonia spontaneously. By a simple slide agglutination method we determined when antibodies first appear in the blood of patients with pneumonia treated with sulfapyridine, and believe that this may indicate when it is safe to discontinue treatment. In 1929 a microscopic slide method was described by Sabin<sup>4</sup> for the detection of specific pneumococcic agglutinin in the blood. Since then, this method has been used as a guide to the adequacy of serum therapy by several physicians having a large experience with pneumonia. There is some difference of opinion, however, concerning the value of the agglutinin test as a guide to serum dosage.<sup>1,2</sup> Some feel that it is too delicate a test; that is, a patient with a strongly positive agglutinin test still may need more serum. It is

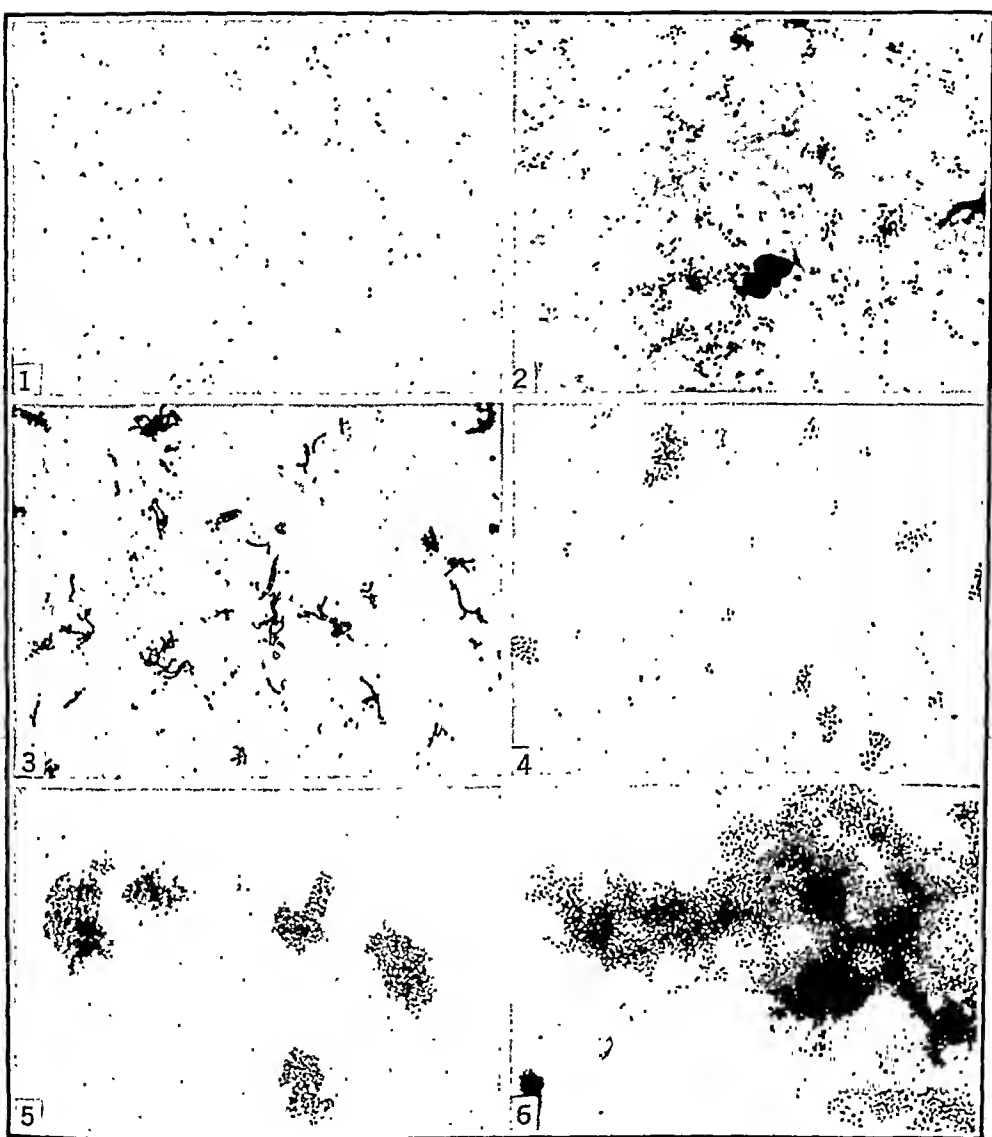


FIG. 1, Negative agglutination. FIG. 2, 1 + agglutination. FIG. 3, 1-2 + agglutination. FIG. 4, 2 + agglutination. FIG. 5, 3 + agglutination. FIG. 6, 4 + agglutination. (Fig. 3 illustrates appearance of test when antigen is "rough," i. e., consists of pneumococci in chains.) Reactions of 2-3 +, or greater, are significant of active specific immunity.





not the purpose of this paper to enter this dispute but to indicate that when specific agglutinin appears in the blood spontaneously in patients who have not received serum, it is a reliable indication of the development of active immunity and as such can be used as a control for the continued administration or withdrawal of sulfapyridine. The final decision depends on the presence or absence of complications.

The present study represents a total of 275 agglutinin tests made at frequent intervals during the course of pneumonia in 50 adult patients treated with sulfapyridine. The slide agglutination technique as described by Sabin was the method used. Blood was collected in a small glass capillary from a puncture of the ear or finger, as in performing a coagulation time. The contents were expelled on a glass slide from the capillary by means of a small rubber bulb (such as accompanies a smallpox vaccination outfit). The clot is easily lifted off with a hot wire, leaving the serum almost

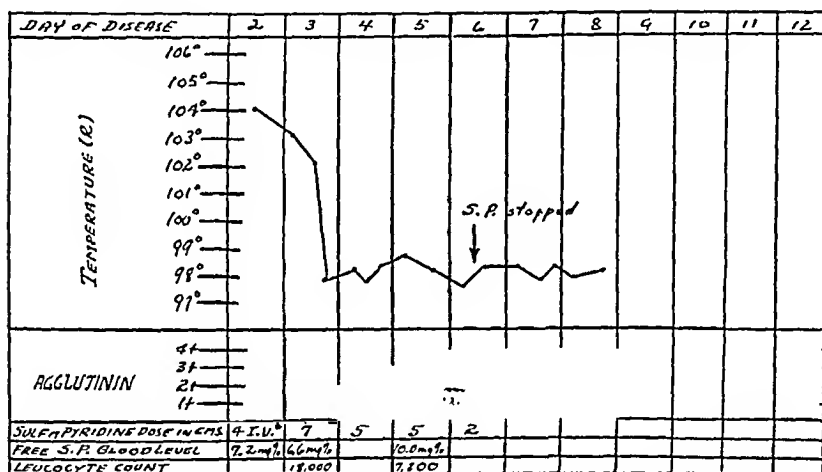


CHART 1.—J. B. ♂ 35 Type I pneumococcic R.L.L.-R.M.L. Pneumonia. Sulfapyridine stopped when agglutinin = 4+

\* Intravenous sodium sulfapyridine.

clear. The test was performed by mixing on a slide a loopful of formalized pneumococci† of the homologous type with a drop of the patient's serum and allowing it to dry in air. The film was fixed with heat and laked by covering it with modified Ruge's solution (4% formaldehyde and 1% acetic acid). It was then rinsed with water, stained with crystal violet or carbol fuchsin, and examined with the oil immersion lens. The degree of agglutination was recorded in accordance with the following scale: 0, 1+, 2+, 3+, 4+; 0 representing no agglutination and 4+ complete agglutination (Charts 1-6).

Charts 1 to 6 illustrate representative cases.

† Suspensions of Types 1 to 30 pneumococcus were supplied by the Lederle Laboratories, Inc.

Charts 1 and 2 are of patients with uncomplicated pneumonia without bacteremia to whom sulfapyridine was administered until the agglutinin test became markedly positive. Uneventful recovery followed.

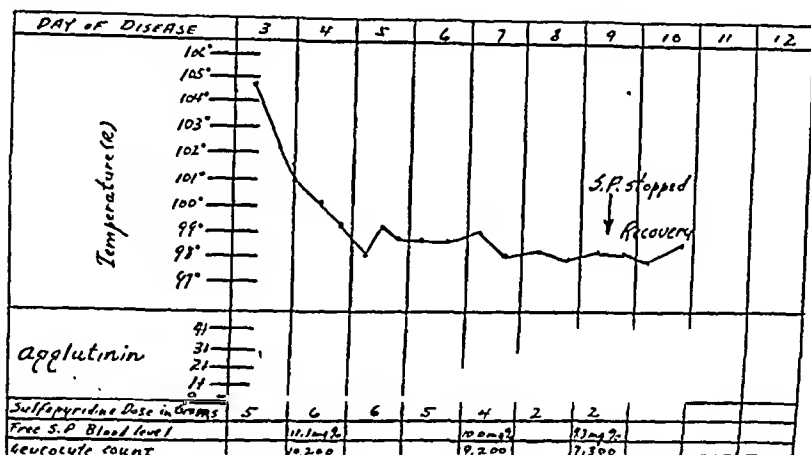


CHART 2.—W. C. ♂ 35 Type I pneumococci R.L.L. pneumonia. Sulfapyridine stopped when marked agglutination occurred.

Chart 3 is that of an uncomplicated pneumonia with bacteremia which persisted for one day after the temperature had dropped to normal. Sulfapyridine was continued until the 11th day of the disease when the agglutinin had become 2+. (At that time also

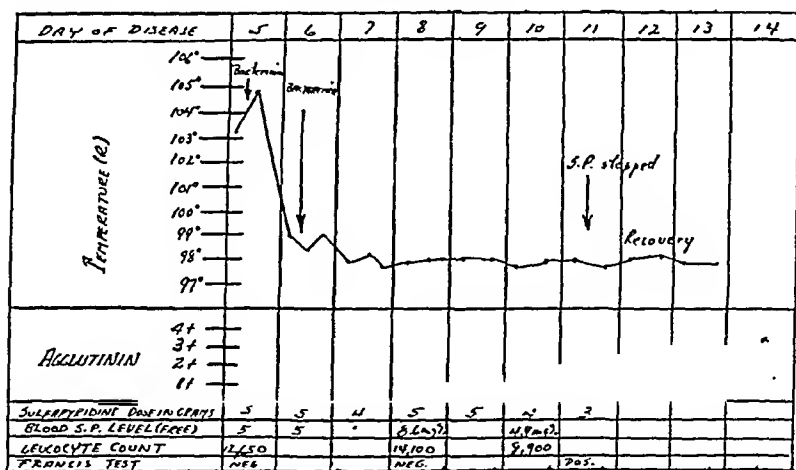


CHART 3.—B. L. ♂ 41 Type VII pneumococci R.U.L. pneumonia with persistent bacteremia. Agglutinins appear late—S. P. continued until agglutinins become strongly positive.

the Francis test with homologous type polysaccharide solution became positive. Both the agglutinin and Francis tests were negative prior to that date. Studies now in progress attempting to

correlate the two tests as indices of active immunity in sulfapyridine-treated pneumonia will be described in a subsequent report.)

Chart 4 is of a patient who, in spite of a high free sulfapyridine level in the blood, had delayed resolution and ran an irregular fever.

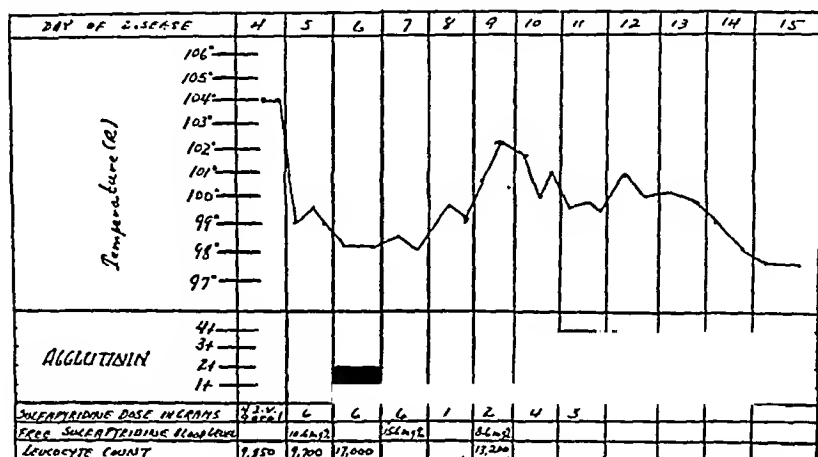
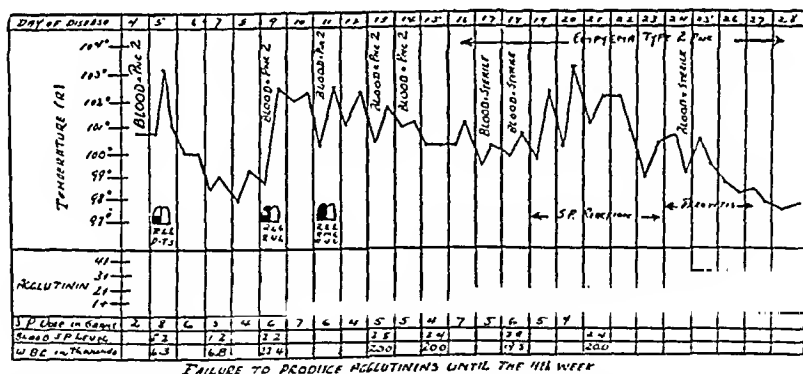


CHART 4.—♂ 27 Type II pneumococcic R.U.L. pneumonia. Irregular fever and delayed resolution, in spite of good sulfapyridine blood level. Sulfapyridine continued until agglutinins became 4+.

Sulfapyridine was not discontinued, therefore, until the 11th day of the disease, at which time the agglutinin test became markedly positive. Thenceforth, recovery was uneventful.

Chart 5 is of a patient with Type II pneumococcic pneumonia,



FAILURE TO PRODUCE AGGLUTININS UNTIL THE 4TH WEEK

CHART 5.—J. N. ♂ 41 Type II pneumococcic pneumonia with persistent bacteremia-spread and empyema. Failure to produce agglutinins until the 4th week. Low blood sulfapyridine level, initial leukopenia, and absence of agglutinin allowed spread of infection.

initial bacteremia and low white blood count. In spite of large oral doses of sulfapyridine, he failed to maintain an adequate blood sulfapyridine level. On the 9th day of his disease the pneumonia spread from the right lower lobe to the right upper lobe and the

blood culture was again positive for Type II pneumococci. For the next 6 days the blood contained Type II pneumococci and during this time the right middle lobe became involved, and finally signs of empyema developed. At no time were agglutinins for Type II pneumococci present in more than 1+ concentration. On the 18th day of the disease they became more definitely positive (2+). On the next day signs of toxic reaction to sulfapyridine first appeared and on the 20th day the drug was withdrawn (somewhat reluctantly for fear of more spread or blood stream invasion). After withdrawal of sulfapyridine, however, the blood remained sterile. On the 27th day, the temperature had returned to normal in spite of recurrent delirium tremens and a mild parotitis. At this time the agglutinins for Type II pneumococci were strongly positive

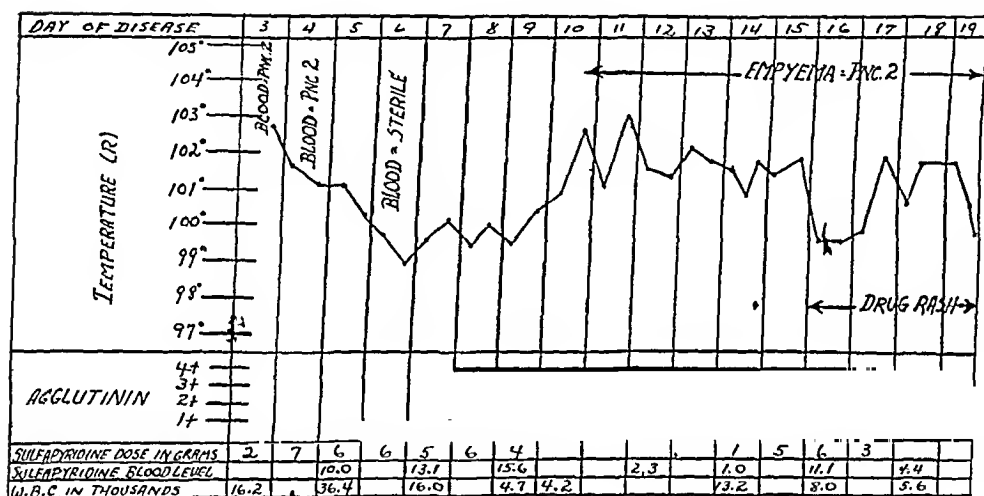


CHART 6.—Type II pneumococcic L.L.L. pneumonia with bacteremia and empyema. Septic complication developed in spite of marked agglutination. Sulfapyridine reaction did not influence agglutinin persistence.

(3+) and the patient went on to complete recovery following drainage of the empyema. We believe this case illustrates the failure of sulfapyridine to produce adequate bacteriostasis due to its low concentration in the blood. This occurred in spite of fairly large oral doses. As a result of the patient's poor body defenses (low leukocyte count early in the disease and failure to develop agglutinins until late in the disease) his course was very stormy. After sulfapyridine was discontinued, however, the patient recovered, for by this time he had a good leukocytosis and definitely positive specific agglutinins for Type II pneumococci in his blood.

Chart 6 is of a patient with Type II lobar pneumonia with bacteremia on admission. In spite of a high free sulfapyridine blood concentration, good early leukocytosis, and the development of

strongly positive agglutination for Type II pneumococci on the 8th day of the disease, empyema developed. This may have been a result of the leukopenia (4700) which appeared on the 9th day of the disease necessitating withdrawal of the drug. When the leukocyte count had risen to 13,000 on the 14th day, sulfapyridine was resumed because of the empyema, but again the leukocyte count fell and this time fever and rash also appeared as further signs of a toxic reaction to sulfapyridine. Uneventful recovery followed surgical drainage of the empyema carried out after the sulfapyridine reaction had subsided on the 20th day.

We believe Charts 5 and 6 illustrate that recovery from pneumonia treated with sulfapyridine requires: 1, adequate sulfapyridine concentration in the blood; 2, maintained leukocytosis; and 3, development of active immunity by the patient in response to his infection. When any one of these factors is inadequate, danger of spread, invasion of the blood stream, and septic complications is greatly increased.

Table 1 indicates that in complicated pneumonias a strongly positive agglutination test was not obtained as early in the course of the disease as in uncomplicated pneumonia. In the complicated cases such a reaction was first obtained on an average of 12.5 days after the onset of the illness, while in the uncomplicated cases, agglutinin appeared on an average of 8.3 days after the onset. We feel that failure to develop active immunity (as indicated by the agglutinin test) by the 9th day of illness was a predisposing factor in the development of complications, and that discontinuing sulfapyridine soon after the initial drop in temperature would have been most dangerous in such cases. When possible, sulfapyridine was continued in all our cases until a good agglutination reaction appeared.

TABLE 1.—RELATION OF COMPLICATIONS TO TIME REQUIRED FOR AGGLUTININ FORMATION.

	Day of disease maximum agglutination.	Average of maximum agglutination.	No. of cases.
Uncomplicated cases . . . . .	8.3	3.1+	27
Complicated cases . . . . .	12.5	3.5+	23
Total cases . . . . .	10.4	3.3+	50

**Summary.** 1. Fifty adult patients with pneumococcic lobar pneumonia treated with sulfapyridine were studied to determine the time at which active immunity first appeared.

2. All patients with proven type-specific pneumococcic pneumonia developed strongly positive agglutinins at some time in the course of their illness.

3. Strong type-specific agglutination occurred in the uncomplicated cases on an average of 8.3 days after the onset of the disease; in complicated cases on an average of 12.5 days.

4. When active immunity did not appear early in the second week of the disease, complications or delay in resolution frequently occurred.

5. Persistence of a strongly positive agglutination for the homologous type pneumococcus was a favorable prognostic sign.

6. Occasionally, empyema developed after a strongly positive agglutination appeared. All such cases, however, had bacteremia on admission and in some cases this persisted for 24 hours or longer after sulfapyridine therapy was begun.

**Conclusions.** 1. We believe that recovery from pneumonia in patients treated with sulfapyridine requires: 1, adequate blood sulfapyridine concentration; 2, maintained leukocytosis, and 3, development of active immunity by the patient in response to his infection.

2. In uncomplicated pneumococcic pneumonias a safe rule appears to be to continue sulfapyridine therapy at a dosage which will produce a blood level above 4 mg. per 100 cc. until a strongly positive microscopic agglutination test is obtained with the patient's serum against pneumococci of the type with which he is infected. In complicated pneumococcic pneumonias sulfapyridine should be continued, if possible, until the temperature and pulse have returned to normal, even though strongly positive agglutination has occurred prior to that time.

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### CONTROL OF URINE REACTION.

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ALTHOUGH there can be no denying that normal kidneys are well equipped to excrete urine at least as acid as pH 5, attempts both medical and otherwise to render this body fluid alkaline are met on every hand. There is, however, growing sentiment against such misdirected effort. Evidence gathered in the laboratory indicates that the kidneys resist interference with the fundamental acid character of the urine and manipulation of its natural variability. Since tampering with urine reaction is undesirable without ade-

quate knowledge of the forces involved, the problem has been approached experimentally with the intention of providing a foundation upon which to base certain phases of medical practice.

**Alteration of Urinary Reaction With Diet.** Since it is commonly assumed that the intake of food is associated with a urinary shift toward alkalinity, a series of tests was conducted on 6 presumably normal laboratory technicians prior to and shortly after the ingestion of a meal. Four of the subjects in a total of 71 tests revealed urinary pH rise in 9 instances, fall in 59, and no change in 3. The other 2 in 65 experiments showed a rise in 37 instances, drop in 16, and no change in 12. There was no apparent dietary cause for this difference. All subjects were in excellent health. The only obvious

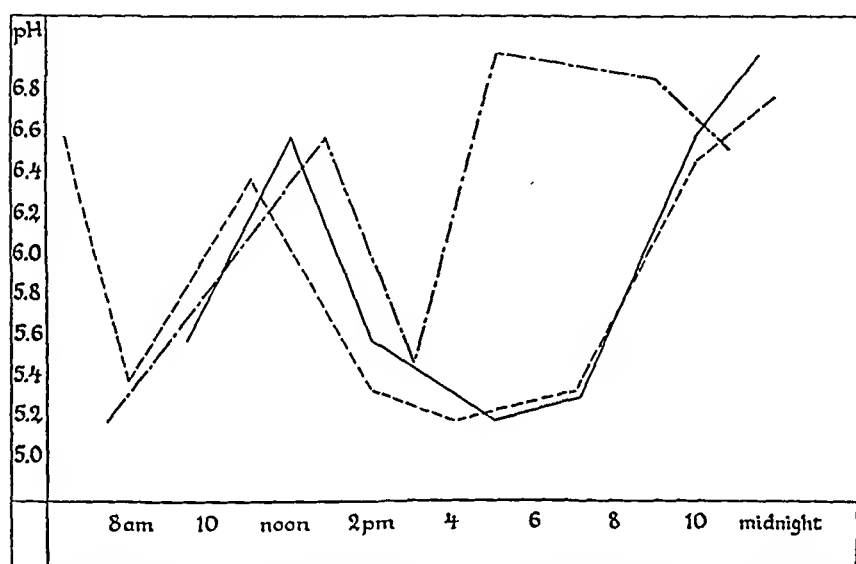


CHART 1.—Urinary pH changes after ingesting one cup of stewed rhubarb. ----- average "normal" curve; ——— after taking rhubarb at 10 A.M.; — · — after taking rhubarb at 3 P.M.

difference was in temperament. The two subjects with tendency toward alkalinity were emotionally calm and deliberate in their actions in contrast to the others who were more "excitable."

In our experiments we have noted that the urinary reaction responds very quickly to certain foods. This response, however, may be masked by changes in the opposite or in the same direction. Rhubarb, for instance, may or may not materially influence the urinary pH (Chart 1).

The food which has most rapidly alkalized the urine in our studies has been cantaloupe. Unlike most of the fruits which are ingested as acid although they give an alkaline ash, cantaloupe is close to neutrality, pH 6.17–7.13.<sup>2</sup> No other food was able to raise the pH to such a high level—7.2 to 7.8.



All data herein presented were obtained by comparison with buffer standards and suitable indicators (bromocresol green, pH 4.5–5.4; chlorphenol red, pH 5.2–6.8; phenol red, pH 6.8–8.0). Potentiometric measurements were occasionally undertaken. The results are given in terms of room temperature; correction to 38° C. requires subtraction of approximately 0.2 pH from observations made at 25° C.

The results of 4 consecutive days of an exceedingly strict alkaline-ash diet are depicted in Chart 2. The usual pH curve is unrecognizable the first day, due largely to cantaloupe at breakfast and lunch. On the second day, when the fruits consisted of banana and pear, the outline of the "natural" curve begins to appear. Cantaloupe at lunch on the third day completely distorts the afternoon portion of the curve, but when this fruit was not eaten until the evening meal on the fourth day, the fundamental curve is readily apparent. Neither the dietitian responsible for the food nor the subject were aware of any special alkalizing effect of cantaloupe before the tests.

It is rather striking that a pH of 4.8 was reached on the second day of this alkalization régime. On other occasions a tendency for the reaction to shift sharply from either extreme limit toward the other has been noted. When the kidneys are confronted with the necessity of excreting extremely acid or alkaline urine, do they continue longer than excess of acid or base would warrant with a subsequent shift in the opposite direction to achieve metabolic equilibrium? It is not unusual to observe decidedly acid urine in the presence of an alkaline-ash diet. In particular, two dietitians who consistently showed pH 5 on arising continued to do so on an alkaline-ash diet.

Attempts were made to ascertain whether or not base was stored in a practical sense on an alkaline-ash diet or lost on an acidic-ash diet. Before breakfast on the fifth day in each series, each subject took 2- or 5-gram doses of sodium bicarbonate every half hour until the urine turned litmus paper lavender or blue. There was no consistent difference in the amount of bicarbonate required (generally 5–10 gm.) after the two diets. The only one out of 8 subjects who did not need to take any bicarbonate on either diet was the subject shown in Charts 2, 3A, 5, and 6. It is recognized, of course, that this experiment proves very little with regard to loss or storage of base, but it does demonstrate that dietary changes may have an astonishingly small effect upon the reaction of the morning urine.

Of a group tested, 4 typical subjects are presented in Chart 3 to show the difference between a well-balanced diet and one in which the lunch was strictly acidic-ash and the dinner alkaline-ash. Fluid at the luncheon was restricted to 90 cc. of cranberry juice which is one of the most effective means of lowering urinary pH. The

purpose was to obtain an exaggerated response, if possible, by avoiding any upward trend attributable to output of fluid. For a similar reason ingestion of extra fluid was encouraged in the

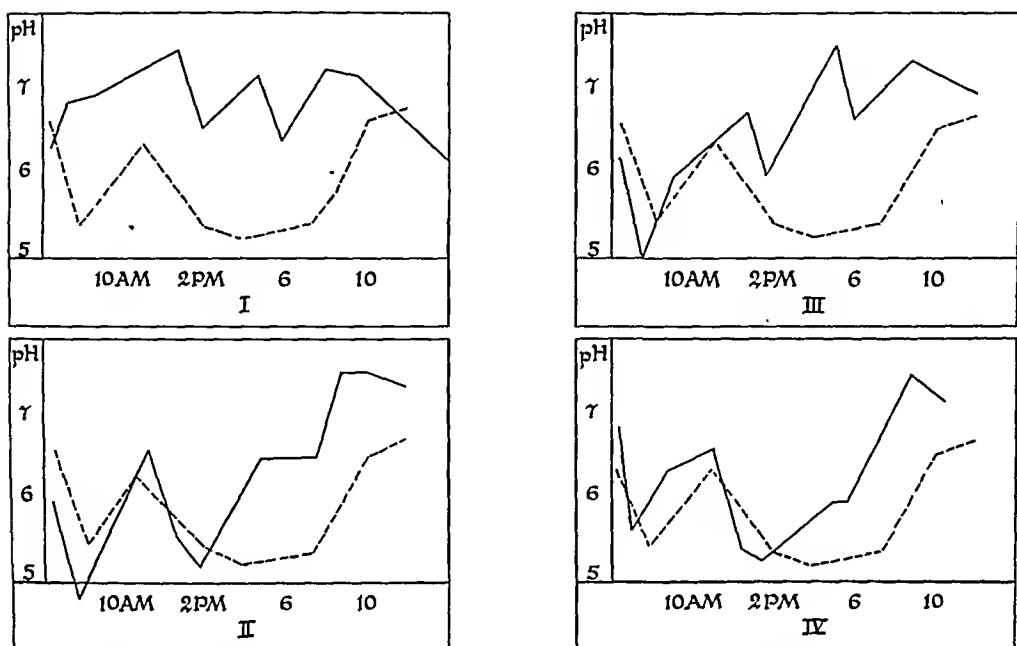


CHART 2.—Urinary pH changes on an alkaline-ash diet. ----- average "normal" curve; ——— changes encountered on specified day of diet.

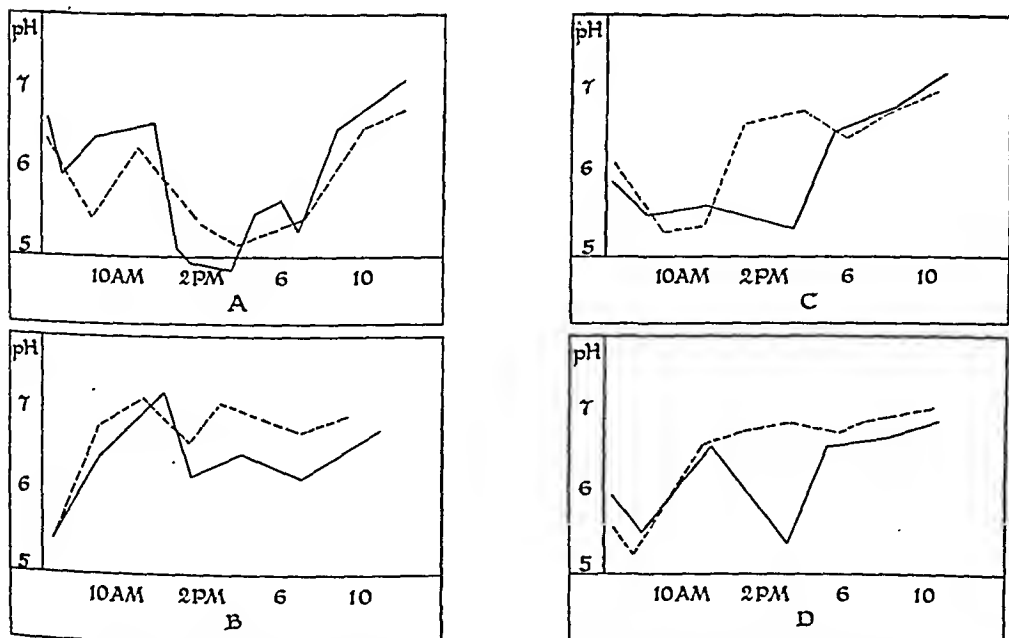


CHART 3.—Urinary pH changes with acidie-ash lunch followed by alkaline-ash dinner. ----- average "normal" curve; ——— response under test conditions.

evening to intensify alkalinization of the urine due to the character of the supper. With 3 of the subjects sharp depression of the pH is seen in the early afternoon, followed by prompt recovery. Subject B, however, shows less acidity but prolongs the depression into the evening. There is no apparent effect of the alkaline-ash supper in any subject.

The curve for Subject A (Chart 3) is not so smooth as the others since specimens were collected more frequently than ordinarily would be voided. It is noteworthy that the drop to unusually low levels is quickly succeeded by an upward trend which overreaches the average curve. The obvious depression at the time of the evening meal is characteristic of this subject on ingesting food. The average curve does not show these depressions since, except for lunch, the major change is in the direction of diminished acidity. Specimens covering the meal period are necessarily small. Even though highly acid, their effect is almost lost in subsequent larger volumes of less acid urine which ordinarily remain in the bladder until micturition occurs.

While it was possible, by taking advantage of the natural trend of the individual, to produce reactions between pH 4.6 and 7.8, these reactions could not be maintained at will with the subject shown in Chart 2. In fact, stubborn efforts at definite acidification or alkalinization were met by erratic and unpredictable changes.

It is not questioned but what 24-hour urine specimens, suitably collected and preserved, would demonstrate a different level on acidic, alkaline, and mixed diets. The reaction of the separately voided specimens presumably provides much more clinically-useful data. We are convinced that any regimen which flattens the daily pH curve, especially in the higher values, is not to be recommended. Many of the recognized end-products of metabolism are acidic and accumulate regardless of diet. Their excretion by means of an acid urine is undoubtedly a normal procedure. Any effort, therefore, to force elaboration of an alkaline urine is bound to be beset with difficulties. It is impossible to excrete a continuously alkaline urine without resorting to large doses of such agents as sodium bicarbonate (excepting those nephritics with fixation at pH 6.8-7.2 and persons with ammoniacal infections).

**Alteration of Urinary Reaction With Drugs.** Experimentally it has been possible to maintain a pH level of approximately 5 for several days by means of drugs and diet. Subsequently, the pH has risen coincident with an increased output of ammonia, regardless of the diet or further administration of acidifying drugs, thus corroborating the findings of others. A typical case is presented in Chart 4 in which only the pH values are followed.

To conserve space, the observations on this patient are plotted in Chart 4 without reference to time. Since voidings were not frequent, the graph represents a period exceeding a month. To

render mandelic acid therapy for bacilluria (*E. coli*) more effective in this case, acidification had been attempted with a hydrochloric-nitric acid mixture.<sup>4</sup> No satisfactory response was noted until an acidic-ash diet was instituted (point A on the graph). Cranberry juice was introduced on the third day of this regimen, but failure of the pH to fall further led to the suggestion that the mineral acids were responsible. Discontinuance of the HCl-HNO<sub>3</sub> mixture resulted in a sharp drop to pH 5 which was maintained for 5 days. Although there was less acid for excretion the pH fell. A total of 750 cc. of water had been required for administration of the acids.

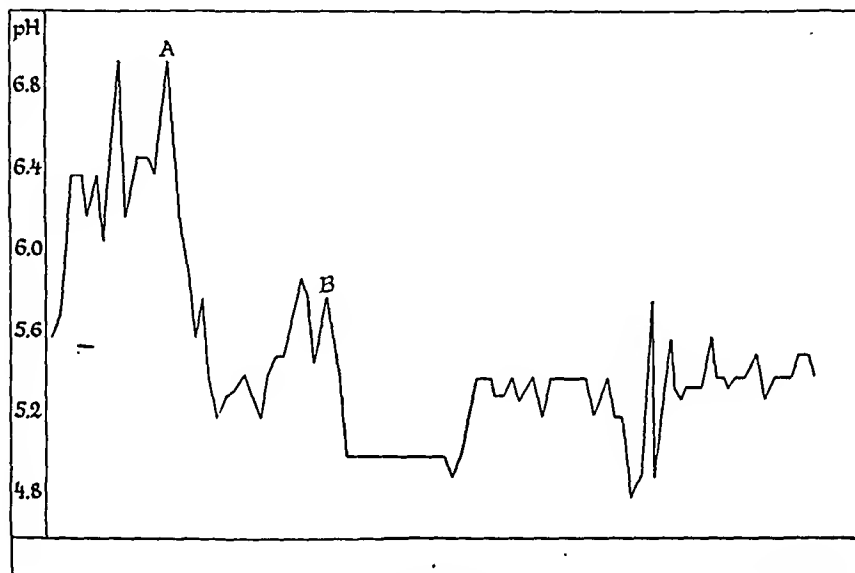


CHART 4.—Urinary pH as affected by drugs and diet. A, Institution of acidic-ash diet; B, discontinuance of HCl-HNO<sub>3</sub> mixture.

Excretion of this otherwise unnecessary water had interfered with the elaboration of a concentrated, and thus more acid, urine. Water as such was withheld and cranberry, plum and prune juices substituted. An effective acidic-ash diet can often be secured in this manner and yet permit the inclusion of a small serving of one green vegetable, cooked or raw, for lunch or dinner.

After 5 days at pH 5, the urine shifted to a higher level despite little relaxation in the acid therapy. Relative fixation is observed in Chart 4 at a less acid reaction. Greater variability also is seen. If intense acidification is therapeutically desirable, it would seem logical to discontinue the treatment as soon as physiologic adjustment sets in and raises the pH.

In Chart 5 is shown the effect of administering sodium benzoate. It is noteworthy that this drug did not lead to acidification of the urine as seen in the curve itself, although there was prompt excretion of hippuric acid (Table 1). Comparison, however, with the

natural curve of the subject reveals that the usual degree of "alkalinity" failed to materialize. Administration of sodium bicarbonate resulted in a definite rise in pH despite the opposite tendency ordinarily.

TABLE 1.—URINARY CHANGES AFTER ADMINISTRATION OF TEST DRUGS.

Time.	Volume, cc.	pH.	Hippuric acid as benzoic, gm.
9 A.M.	40	5.0	
9.05 A.M.	<i>Administration of benzoic acid (5.8 gm. in 180 cc. of water)</i>		
10 A.M.	67	5.7	0.89
11.15 A.M.	116	5.8	1.40
NOON	66	5.4	1.67
1.05 P.M.	57	5.2	0.88
			4.84 (total)
(No lunch permitted)			
1.10 P.M.	<i>Administration of NaHCO<sub>3</sub> (4 gm. in 200 cc. of water)</i>		
3 P.M.	50	5.4	
4 P.M.	15	6.2	
5 P.M.	15	7.2	
5.25 P.M.	8	6.9	

Chart 6 shows the same subject under mandelic acid. Although this drug did not affect the morning "alkaline" peak, it had a slight lowering effect during the afternoon when taken in conjunction with a substantially acidic-ash lunch. Without provocation, however, the pH rose to an unusually high level after an early dinner (mixed diet)—which is an instance of behavior previously mentioned.

**Predetermining the Reaction.** It is often taken for granted that the reaction of the urine can be altered at will. In 100 experiments upon one subject it was attempted to predict the urinary pH by controlling the supposed factors in its production. The majority were complete failures. The diet was planned to force the excretion of highly acid or strongly alkaline urine without much success. Not until it was recognized that there was a fundamental acid-base rhythm was it possible to shift the pH in the desired direction, and then only by taking advantage of the rhythm. All efforts to reach a very low pH were unsuccessful except those which coincided with the lowest level of the "natural" curve, that is, in the early afternoon. Likewise, the highest values for pH could be obtained only in coincidence with the morning or evening peak of diminished acidity.

The normal individual experiences a variation in urinary pH such that definite decrease in acidity occurs at some time between 9 A.M. and midnight. The urine may or may not become actually alkaline. The time of the peak of diminished acidity is more or less characteristic of the individual. Likewise, the entire curve for 24 hours tends to assume a similar pattern day after day—so much so that in a limited group, once the trend is known, it is possible to identify unlabelled curves. For example, 6 dietitians living under the same roof and partaking of the same general diet presented 6 different

curves which persisted in spite of deliberate alteration in the acid-base residue of the diet. Again, upon a group of inmates of a prison hospital; curves were obtained on repeated testing which were consistently alike for the individual, yet different from each other. Likewise, a group of technicians and students on 3-day test periods

CHART 5.

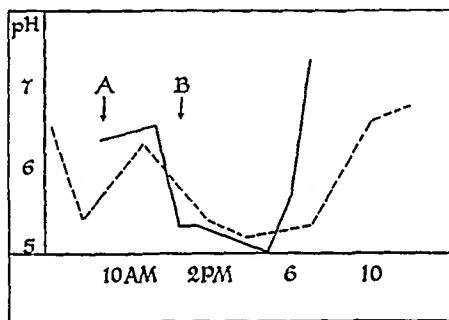
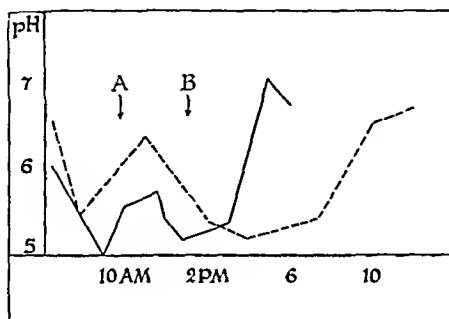


CHART 6.

CHART 5.—Urinary pH changes after test drugs. A, 5.8 gm. of sodium benzoate; B, 4 gm. of sodium bicarbonate (see also Table 1).

CHART 6.—Urinary pH changes after ammonium mandelate. A and B, 0.5 gm. doses.

presented striking similarity for a given subject and dissimilarity with others in the group. Typical curves are shown in Chart 7.

Our observations convince us of the presence of a natural rhythm characteristic of the individual which is the result of manifold factors and which tends to manifest itself despite efforts to alter it. Although this point of view has been given little place in the literature, it has not escaped the notice of others. Particular reference should be made to Obermer of London<sup>7</sup> who, on examination of our individual curves, not only confirmed our impressions but went so far as to suggest that the urinary pH curve for the 24-hour period was a physiologic characteristic comparable, after a chemical fashion, with finger prints.

The curve will not invariably follow the same pattern under all conditions (therein lies its usefulness), but *this basic variation will impose itself upon accidentally or intentionally produced urinary changes*. Neglect of this fact or ignorance regarding the form of the

individual curve can only lead to conclusions which, at best, are not warranted and which, at worst, are wholly fallacious.

It is not intended to create the impression that the urinary pH curve is so uniform that its similarity is apparent to the most casual observer—quite the contrary. If specimens are obtained frequently, minor variations may obscure the general trend, but when such

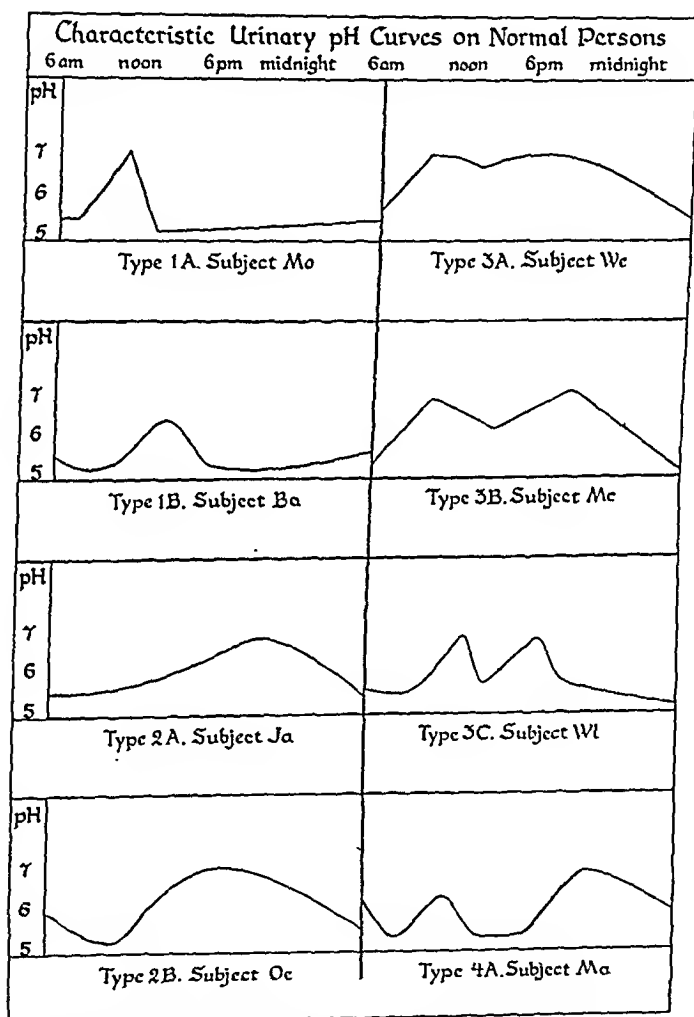


CHART 7.—Typical urinary pH curves representing the fundamental acid-base rhythm of various subjects.

curves are superimposed upon others from the same person and viewed by transmitted light, the fundamental change in each is more evident.

Some subjects show marked persistence in the urinary pH curve while others deviate on comparatively slight provocation. The greatest variability was shown in the youngest group studied: 10

college undergraduates. It would appear that capricious eating habits, the conflict and strain attendant upon assignments and quizzes, "dates" and general restlessness contribute much to the changeableness of the urinary curves. It must be admitted, however, that one of the most consistent curves encountered was in this group; for the 12 consecutive days of the test this girl showed no variation in the form of the curve.

The present state of our knowledge does not permit a complete listing of all the factors which enter into the composite urinary pH curve. It is generally assumed that the chief factor influencing the excretion of acid by the kidney is the elaboration of HCl in the stomach<sup>5</sup> although experimental evidence is far from substantiating this claim. Other factors usually stressed include fluid intake, diet, and changes in the respiratory center.<sup>3</sup> Alteration of the normal course of events, such as development of a cold or the taking of an effective saline cathartic, may manifest itself in conspicuous fashion in the urinary pH curve. Although hyperventilation *per se* leads to increased alkalinity, exercise intensifies the acidity of the urine. According to Obermer:<sup>7</sup> "Insofar as it is possible to correlate two independent variables without taking a host of others into consideration, fatigue tends to make the pH more alkaline, rather than more acid." The behavior of the thyroid gland may be an important means of altering urinary reaction. Possibly emotional and mental states play a far greater rôle than is realized. Numerous illustrations could be culled from our studies, but two will suffice: 1, A student who presented an extraordinarily flat and highly acid curve day after day excreted decidedly alkaline urine when she received news of serious illness at home; 2, a patient who showed unexpected departure from his usual curve was startled by being asked what happened at a specified hour; he had had occasion to reprimand his children at that time.

Among readily determinable factors which affect the urine reaction, availability of water for excretion is noteworthy. A series of 97 tests upon urine obtained without motive is described in Table 2.

TABLE 2.—RELATIONSHIP BETWEEN RATE OF URINE FLOW AND PH.

No. of observations.	Urine flow.	pH range.
43 . . . . .	1 cc. per minute or less	4.8-5.8
23 . . . . .	1 cc. per minute or less	6.0-7.0
6 . . . . .	1.1-3.8 cc. per minute	5.3-5.7
25 . . . . .	1.1-3.8 cc. per minute	6.0-7.3

From this group are excluded all first morning specimens since urine is normally formed at a diminished rate during sleep at a reaction which possibly is somewhat typical of the individual. Although apparently the majority of normal persons excrete a decidedly acid morning urine, such a finding is unusual for this subject (Chart 2). The 13 night specimens in the series from which



these data are drawn were all below 1 cc. per minute, yet 9 of them varied from pH 6.5 to 6.9, the remaining 4 between 6.0 and 6.4.

Water ingested and not needed by the normal body is promptly (depending on the time of day) excreted in a dilute urine, the pH drifting upward. Similarly, lack of water for excretion is generally associated with highly acid urine. By experimental planning, however, the urine was forced in seven instances to a pH of 7.2-7.8 when the volume amounted to 1 cc. per minute or less. On the other hand, diuresis was produced with grape juice (500 cc. diluted with water to 1 liter and ingested within 90 minutes) yet the pH remained low, the results being given in Table 3. Cranberry, plum, and prune juices also tend to drive the pH downward while the rate of urine formation increases.

TABLE 3.—EFFECT OF INGESTING AN EXCESSIVE AMOUNT OF GRAPE JUICE.

Urine flow.	pH.
1.2 cc. per minute	5.3
2.5	5.6
3.4	5.7
6.2	5.7
6.5	5.4
7.0	5.0
9.5	5.7

The tendency for volume increase to be associated with elevation of pH is frequently ignored. When 500 cc. of water are given in lieu of breakfast for the production of an "alkaline tide," the diminished urinary acidity often encountered may merely reflect the increased output of fluid. Conversely, if the amount of water eliminated is small, the pH may remain at a low level and a "tide" be declared absent and attributed to lack of gastric acid! Hubbard *et al.*<sup>5</sup> report but do not consider the urinary volumes when investigating pH variations with and without breakfast, but the differences in fluid output are as striking as the changes in pH.

The tense attitude assumed by a runner about to start a race causes a drop in urine volume (MacKeith *et al.*, 1924). Wilson<sup>10</sup> tried to eliminate the decrease in urine volume by water drinking, but frequently without success. Even with 200 cc. of water every 30 minutes for 2 hours preceding and extending through the period of exercise, the urine volume still fell to less than one-seventh that of the fore-period. After 1 to 2 minutes of strenuous exercise, the diminished water output was accompanied by increase in hydrogen-ion concentration, titratable acidity, and ammonia output. The urine was collected at 10-minute intervals or less. The maximum change was reached within half an hour, followed by return to "normal" in 40 to 90 minutes.

The rate of water excretion varies throughout the 24 hours. Simpson and Wells<sup>9</sup> attempted with dogs to get a uniform excretion but failed. Regardless of the intake of 100 to 200 cc. of fluid hourly,

Simpson<sup>8</sup> obtained a negative water balance during part of the day and water retention at night during sleep. The acid retention period ended about 7 A.M., the subsequent polyuria being accompanied by relatively high pH. A marked decrease in urinary volume was encountered by Simpson between 2 and 6 P.M. and a second maximum between 6 and 9 P.M. According to Best and Taylor<sup>1</sup> the urine volume during the day (8.30 A.M. to 8.30 P.M.) is 2 to 4 times that of the night. The ratio holds, even if the quantity of fluid taken during both periods is the same.

**Pathologic Fixation of Urinary pH.** Efforts to control the reaction of the urine are frequently disappointing. In normal individuals it is often surprisingly difficult to fix the pH by diet or drugs. It is equally difficult to alter the pH when disease fixes it. Attempts to do so are not necessarily in the best interests of the patient. Although highly acid urine may be seen early in nephritis, progressive impairment gradually raises the level of fixation to neutrality foreshadowing the fatal termination of the disease. Unusual acidity has been noted<sup>6</sup> in cardiac decompensation when the urine output is low; release of the edema fluid with consequent upward shift in the pH occurs as the patient improves. We have observed fixation of pH below 5 in cardinals.

The statistical study of Ziegler and Brice<sup>11</sup> warrants the conclusion that "the ability of the kidney to excrete solids and to concentrate the urine is greater when the urine is acid than when it is alkaline or neutral." According to these investigators, acid urines show fewer abnormal findings than those which are alkaline or neutral and emphasis is placed upon the undeniable fact that the human kidney is phylogenetically adapted to excrete an acid urine.

**Summary.** 1. The urinary pH cannot be consistently changed at will without regard for its natural trend.

2. The acidifying or alkalizing effect of test substances cannot be judged solely by the urinary pH observed. Comparison with the fundamental or natural curve is necessary.

3. The natural acid-base curve can be distorted by dietary factors with variable ease in different subjects.

4. The determination of urinary pH following meals is of no practical clinical value.

5. It has not been possible by dietary measures to produce continuously alkaline urine.

6. Temporary elevation of urinary pH is most readily secured with cantaloupe.

7. The easiest means of maintaining acid urine in the normal individual is the substitution of cranberry juice for water as such in the diet.

8. The effective action of acidifying drugs is conditioned by the amount of water simultaneously claiming excretion.

9. Although concentration of urine is regularly associated with

increasing acidity and dilution with increasing alkalinity, the normal kidney can excrete a highly acid dilute urine and a definitely alkaline concentrated urine. The elimination of water is not constant throughout the day, thus influencing the urinary pH.

10. Emotional and mental states demonstrably affect urinary pH.

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### EFFECT OF NICOTINIC ACID ON PERIPHERAL BLOOD FLOW IN MAN.\*

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In a number of the reports upon the use of nicotinic acid in the treatment of pellagra<sup>5,7,8</sup> the appearance of such cutaneous manifestations as burning, itching, flushing of the face and trunk, and a feeling of warmth has been noted. These symptoms generally were present following the administration of at least 200 mg. of the drug orally or 5 to 25 mg. intravenously. Coincident with the onset of the above symptoms, Spies and his associates<sup>3,7</sup> found an increase in skin temperature which was most marked over the ears, face and neck, less pronounced over the trunk and least over the extremities. Papkin<sup>6</sup> has recently reported rather inconstant surface temperature readings following the administration of smaller quantities of the drug. Since these reactions are obviously vascular in nature, it was considered of interest to investigate the influence of nicotinic acid on peripheral blood flow by means of plethysmographic studies.

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**Method.** Twenty-eight experiments were performed on 15 adult subjects who had been maintained on well balanced diets. Nicotinic acid was given by mouth except in 5 instances in which it was administered intravenously. The plethysmographs and technique utilized were similar in all respects to those described previously by one of us.<sup>2a,b,4</sup> Generally a contralateral hand and forearm, or forearm and leg, were studied simultaneously. The room temperature, except where otherwise indicated, was between 25 and 27° C. and the bath temperature (*i. e.*, temperature of water in the plethysmograph) was 32° C. All readings were calculated as cc. of blood flow per minute per 100 cc. of limb volume. After a control level was determined over a period of 30 minutes, nicotinic acid was administered and blood flow records were obtained (from 5 to 10 in each period) at approximately 15-minute intervals for the subsequent 70 to 150 minutes. The onset and duration of the various symptoms were noted and blood pressure and pulse rate were recorded at intervals during the experiment. In six experiments, skin temperature readings were obtained by means of a Tycos dermatherm.

As reported by previous investigators,<sup>7</sup> the oral dosage of the drug necessary to produce symptoms varied markedly in different subjects and even in the same subject on different occasions. More consistent results were obtained if the procedure was performed in the post-absorptive period; the effective oral dosage under these circumstances ranged between 100 and 300 mg. On the 5 occasions in which the drug was injected intravenously, 20 to 25 mg. were used, in each instance definite symptoms being elicited.

**Results.** *Effect Upon the Hand.* With oral administration, a significant increase in blood flow to the hand was noted in 16 out of 19 instances (Table 1). The maximal flow attained in these experiments averaged 2.2 times the control level. In one of the remaining cases (Expt. 8) there was only a slight increase, but in this experiment the initial flow was much above the normal level due to a high room temperature (32° C.). In two instances (Expts. 17 and 18) in which no change in hand flow was noted, a significant increase in forearm flow was present. The maximal effect in the hand occurred in from 15 to 155 minutes following the administration of the drug. The duration of the increased flow over control readings averaged 75 minutes, the experiments being frequently terminated before the control level had again been reached (Chart 1). In a number of instances, a transient decrease in blood flow occurred from 10 to 70 minutes after administration; generally it preceded the increase.

In 1 of 3 experiments in which nicotinic acid was injected intravenously, a transient rise in flow to the hand (1.3 times) was noted about  $4\frac{1}{2}$  minutes after administration (Expt. 25). However, in this instance as well as in the other 2 experiments, the predominating effect was a decrease in flow to the hand despite the fact that in each case there was an increase in the forearm or leg studied simultaneously.

*Effect Upon the Forearm.* With oral administration of nicotinic acid, a significant increase in blood flow to the forearm was noted in

15 out of 19 instances (Table 1). The maximal flow attained in these experiments averaged 2.5 times the control level. Of the remaining cases, in one (Expt. 6) there was a slight rise and in another (Expt. 21) a significant but transient rise. In two (Expts. 12 and 20) in

TABLE 1.—EFFECT OF NICOTINIC ACID ON PERIPHERAL BLOOD FLOW.

A. Oral Route.

Subject.	Experiment.	Dosage (mg.).	Extremity.	Control blood flow.	After nicotinic acid.			Extremity.	Control blood flow.	After nicotinic acid.		
					Maximal increase.	Time of maximal effect (min.).	Duration of increase in flow (min.).			Maximal increase.	Time of maximal effect (min.).	Duration of increase in flow (min.).
M. F.	1	100	H	4.1	11.7	90	50-110	F	1.2	2.7	110	10-110
D. F.	2	100	H	7.1	14.1	40	20-70	F	2.1	4.2	60	20-70
	3	100	H	8.9	16.0	90	60-100	F	2.2	5.4	100	75-100
D. A.	4	150	H	3.2	11.7	155	40-155	F	1.0	1.7	150	135-150
	5	225	H	8.1	13.0	70	40-90	F	1.4	4.2	40	17-80
	6	275	L	0.8	1.0	54	54-80	F	1.9	2.3	25	15-60
	7	300	H	3.2	6.5	45	35-75	L	0.9	0.9	..	....
	8	100	H	21.6	26.6	30	30-60	F	1.6	6.7	60	20-90
K. K.	9	200	L	1.1	2.0	70	20-90	F	0.8	3.3	60	30-90
	10	100	H	5.7	13.7	120	90-120	F	1.1	2.9	120	70-120
	11	100	H	2.7	17.3	150	30-150	F	1.1	2.1	90	60-150
L. S.	12	100	H	6.3	13.4	140	80-150	F	2.9	2.9	..	....
	13	200	L	0.9	1.1	60	30-70	F	1.9	4.2	50	30-110
C. H.	14	200	H	3.0	8.0	120	35-120	F	1.0	1.83	35	20-120
M. B.	15	150	H	11.6	16.3	15	5-30	F	1.2	2.1	60	15-80
D. D.	16	225	H	8.9	16.6	30	10-80	L	3.9	4.3	80	30-80
D. C.	17	225	H	14.7	14.9	..	....	F	2.7	4.1	18	18-80
J. N.	18	200	H	7.0	7.0	..	....	F	1.7	2.7	60	30-160
G. G.	19	150	L	2.4	2.8	30	10-120					
	20	175	H	7.7	13.6	70	30-100	F	3.4	3.4	..	....
P. A.	21	175	H	3.5	8.9	120	30-120	F	1.5	2.7	20	10-20
M. G.	22	200	H	1.3	3.1	57	30-84	L	0.8	1.1	70	60-80
D. S.	23	225	H	9.3	12.8	22	15-65	F	2.6	9.6	56	12-75

B. Intravenous Route.

J. N.	24	25	H	10.6	9.7	..	....	F	1.4	4.0	5	2-110
	25	25	H	10.1	13.1	4½	1-12	L	3.6	5.6	4½	....
F. S.	26	20	H	13.8	7.7	..	....	F	1.05	3.7	30	5-60
K. K.	27	20	L	0.8	1.4	50	8-80	F	1.3	2.4	32	8-80
M. G.	28	25	L	1.8	1.7	..	....	F	1.5	2.8	2	2-45

All blood flow figures are in cc. per min. per 100 cc. of limb volume.

H = hand; L = leg; F = forearm.

which no change in blood flow was observed in the forearm, a significant increase was present in the hand. The maximal effect in the forearm occurred in from 20 to 150 minutes (average 70 minutes) after the administration of the drug; the duration of increase over control level averaged 66 minutes.

In 4 instances in which the effect of intravenous injection of the drug was studied, a significant increase consistently took place in the forearm. The maximal flow attained averaged 2.5 times the control level, the augmentation continuing for from 43 to 108 minutes after administration.

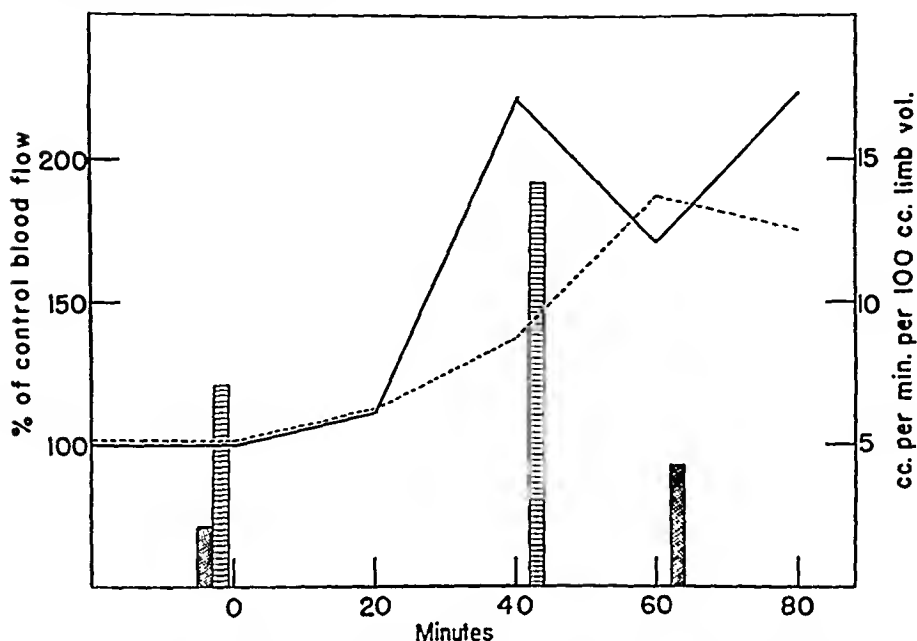


CHART 1.—Effect of the oral administration of 100 mg. of nicotinic acid upon blood flow in hand (solid line) and forearm (dotted line) in subject D. F. (Expt. 2). The lines represent percentage change in flow as compared with the controls. Horizontal-lined column: hand blood flow in cc. per minute per 100 cc. limb vol. Cross-hatched column: forearm blood flow in cc. per minute per 100 cc. limb vol. Bath temp. 32° C.; room temp. 26° C.

*Effect Upon the Leg.* With oral administration of nicotinic acid, only a slight or no increase in blood flow to the leg was noted in the seven subjects thus tested. The maximal flow attained in these experiments averaged 1.3 times the control level (Table 1). Generally, the contralateral forearm, tested simultaneously, showed a significant increase in flow. The intravenous injection of the drug, studied in three instances, resulted in an increase of blood flow to the leg of 1.7 and 1.5 times the control level in 2 experiments, and no effect in the remaining one.

*Effect Upon Blood Pressure and Pulse.* For the most part, blood pressure and pulse rate were very little affected by either the oral or intravenous administration of nicotinic acid. In 4 instances, there was an average rise of 4 mm. in systolic pressure, in 6 an average fall of 6 mm., and in 4 no change. In 5 instances there was an average rise of 5 mm. in diastolic pressure, in 2 an average drop of 5 mm., and in 7 no change. At the time when the maximal increase in blood flow to the extremities was noted, the blood pressure

was generally at approximately the same level as the control readings. The pulse rate change varied from an average increase of 3 beats per minute to an average decrease of 10 beats.

*Effect Upon Skin Temperature.* In 6 experiments, skin temperature readings were obtained from the forehead and the extremities simultaneously with blood-flow determinations. The changes in the forehead showed no consistent trend and in no case were they significant. Likewise with the forearm, very little alteration in skin temperature was encountered, despite the fact that in this site definite increases in blood flow were consistently noted. The same findings were also present for the hand.

*Cutaneous Manifestations.* A correlation between the degree and intensity of flushing of the face and the magnitude of the change in peripheral blood flow to the hand and forearm could generally be noted. With oral administration the only exceptions consisted of one instance (Expt. 17) in which a moderate flushing of the face was present, but no change in blood flow to the hand (that to the forearm being increased), and of another case (Expt. 21) in which no symptoms were observed, but still there was an increase in flow to both hand and forearm (the effect in the latter being transient). Of the remaining 21 instances, in 18 there was a definite flushing present together with a significant increase in flow to the extremities, while in the other 3, minor symptoms were observed and an increase in flow was limited to only one of the two limbs studied (Expts. 12, 18 and 20). In 7 experiments on 4 subjects (not included in the table) neither symptoms nor changes in blood flow in the hand or forearm were noted following the oral administration of the nicotinic acid; in each instance the drug was taken shortly after a meal. When 2 of these subjects were retested using the intravenous route, significant changes in blood flow, accompanied by definite generalized flushing, were elicited. Conversely, in one subject, intravenous injection of 20 mg. of nicotinic acid elicited no or very slight symptoms and no change in blood flow, while oral administration produced definite peripheral vascular responses.

Besides the flushing of the face, which generally was the predominating symptom, in a number of instances the trunk, abdomen and extremities were also involved in the response. When flushing of the limbs was present, it was usually noticed some time after the face and neck were affected, and similarly it remained for some time after the flush had disappeared from the latter sites. Accompanying the flushing were the feeling of general body warmth, itching and stiffness of the face, thumping in the head, slight headache and in 3 instances, pain in the abdomen which was transient. These symptoms generally appeared within 10 to 45 minutes after the oral administration of the drug and within 1 to 3 minutes when the intravenous route was used, most of them persisting for from 40 to 70 minutes. In the case of the intravenous administration, a

transient metallic taste was experienced by some of the subjects within 10 seconds after injection. These findings are for the most part in accord with those reported by others.<sup>7</sup> In no experiment were toxic symptoms encountered with the dosage used in the study.

**Discussion.** On the basis of the above data, it can be stated that the administration of nicotinic acid to subjects on well balanced diets results in a significant increase in blood flow to the hand and forearm. Since these changes in peripheral flow are not accompanied by any definite or consistent alterations in blood pressure or pulse, the probability exists that the increase in flow is due to local changes in the blood-vessels at the periphery rather than to an increase in cardiac output. The finding of an increase in total blood flow through the forearm and the hand without any concomitant rise in skin temperature in these sites suggests that the predominating effect is not upon the cutaneous vessels but rather upon those in the muscles. These observations indicate therefore that the absence of a significant change in skin temperature does not necessarily imply that there has been no alteration in total blood flow to an extremity. Such an assumption has recently been made in a study upon the peripheral vascular effects of nicotinic acid.<sup>6</sup>

Judging from the results obtained in those individuals in whom repeated tests were made and also in one subject who received daily doses of nicotinic acid for about 3 weeks (not included in Table 1), it appears that a tolerance for this drug is not developed. However, as mentioned before, the dosage necessary to produce symptoms and changes in blood flow varies even in the same subject on different occasions. The explanation for the more consistent results obtained when the drug was given on an empty stomach may be that a certain concentration in the body is necessary in order to elicit the peripheral vascular responses. Probably the absorption of the drug shortly after a meal is too slow for the establishment of the proper blood level. Inasmuch as changes in blood flow were produced by oral administration, there is no advantage to the intravenous route, especially since on the three occasions in which the hand was studied under the latter conditions, a decrease in flow to this portion of the extremity was observed simultaneously with an increase to the forearm or leg. Since it has been shown that the blood-vessels in the hand respond by marked constriction to various types of stimuli,<sup>1</sup> it is likely that the fear and apprehension, associated with the procedure of intravenous injection, were responsible for these results.

In view of the fact, therefore, that significant increases in blood flow to the hand and forearm can be produced by the oral administration of therapeutic amounts of nicotinic acid, this drug may have a place in the treatment of conditions in which an increased blood supply to the extremities is desired.



**Summary.** The peripheral vascular effects of nicotinic acid were studied by means of the plethysmographic method in a series of 15 subjects maintained on well balanced diets. It was found that a significant increase in blood flow was generally elicited in the hand and forearm, with only a slight increase in the leg.

Since the changes in peripheral circulation were not accompanied by any definite or consistent alteration in blood pressure or pulse rate, it is probable that the effect was due to local changes in the blood-vessels rather than to an increase in cardiac output.

The possibility is therefore offered that nicotinic acid may be of use in the treatment of extremities with diminished blood supply.

The authors wish to express their appreciation to Dr. Moses Salzer, at whose suggestion this study was undertaken, and to Dr. Harry Salzer, for his coöperation in supplying subjects.

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## THE UTILIZATION OF VITAMIN A ADDED TO MINERAL OIL.

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ONE of the major objections to the use of mineral oil as a laxative or as a substitute for absorbable fat in reduction diets, is due to the preferential solubility of carotene in it and the subsequent loss of the carotene with the excretion of the mineral oil in the stool. This fact has been demonstrated by animal experiments<sup>1,4,6-8,10</sup> and also by studies on human subjects.<sup>2,3</sup> It makes little difference whether the mineral oil is plain or one of the emulsified types whose liquid petrolatum content is less. The preferential solubility of carotene in mineral oil is so great that at body temperature 100 cc. of plain mineral oil could hold as many as 466,666 units of vitamin A in the form of carotene.<sup>2</sup> Amounts of mineral oil as small as 15 or 30 cc. would still be able to remove all of the carotene from a normal diet if the oil came in intimate contact with the food substances containing the carotene.

An attempt was made by one of us<sup>2</sup> to alleviate this objection to the use of mineral oil by presaturating it with carotene and then giving it to a group of patients. Although the precarotene saturated oil protected the ingested carotene from solubility in the mineral oil the compound was grossly changed in color and taste. The cost of adding sufficient carotene to saturate mineral oil at body temperature would be prohibitive.

In one of the early experiments done by Moness and Christiansen<sup>8</sup> on this subject, it was shown that the utilization of vitamin A was not altered by mineral oil if the vitamin A was given as cod liver oil. At this time, however, it was not known that carotene and vitamin A were different substances and the initial workers<sup>1,4</sup> had used butter fat as a source of vitamin A rather than cod liver oil. After Moore<sup>9</sup> reported that vitamin A and carotene were different substances Dutcher, Harris, Hartzler and Guerrant<sup>5</sup> showed that carotene in corn oil was not utilized in the presence of mineral oil but a carefully prepared pigment-free vitamin A concentrate was utilized readily when fed with mineral oil.

This difference in the effect of mineral oil on the preferential solubility of carotene and of vitamin A in oil suggested to us that it might be possible to make a mixture of mineral oil and vitamin A which could be fed to vitamin A deficient rats and by this method to determine whether the animals could remove any, a part, or all of the vitamin A from the mineral oil.

**Method.** Four groups of rats, totalling 30 in number and representing four litters, varying in ages from 28 to 32 days, were put on the following vitamin A depletion diet:<sup>6</sup>

Food substance.	% by weight.	% calories.
Casein, extracted . . . . .	18	16
Starch (Kingsford's) . . . . .	63	55
Salts (Osborne and Mendel, 1919) . . . . .	4	
Hydrogenated vegetable oil (Crisco) . . . . .	15	29
Yeast, 400 mg. daily.		

Five of the rats, chosen from each of the four litters employed and represented as Group I, were used as controls and remained on this diet throughout the depletion period and until death.

Eight rats comprising Group II were allowed to remain on the diet until the signs of depletion occurred by loss of weight or xerophthalmia or both. Four were then given 0.5 cc. of mineral oil containing 2 units of vitamin A daily and 4 were given 0.5 cc. of cottonseed oil containing 2 units of vitamin A daily.

Group III consisted of 10 rats that were given the depletion diet until signs of vitamin A deficiency occurred. Four were then given 4 units of vitamin in 0.5 cc. of cottonseed oil daily and 6 were given 4 units of vitamin A in 0.5 cc. of mineral oil daily.

Group IV consisted of 7 animals. They followed the same regimen as Groups II and III except that 3 received 6 units daily of vitamin A in 0.5 cc. of cottonseed oil, and 4 received 6 units daily of vitamin A in 0.5 cc. mineral oil.

The source of vitamin A was a fish liver oil concentrate containing 190,000 units of vitamin A in each gram of oil. The concentrated fish liver oil was diluted with mineral oil and cottonseed oil until stock solutions were obtained containing 2, 4, and 6 units of vitamin A in each 0.5 cc. of mineral oil and cottonseed oil. The stock solutions of both were kept in the ice box except when being used.

The 0.5 cc. doses of cotton seed oil with vitamin A and mineral oil with vitamin A were administered to the rats by adding the mixture to the yeast powder and making a soft pill out of it. The rats ate this mixture readily and usually at once.

The stools of the rats receiving cottonseed oil were normal. The rats receiving mineral oil had large, greasy and more numerous stools.

All animals, except the control group, were continued for 70 days each on cottonseed oil or mineral oil to which was added vitamin A after signs of depletion had appeared.

**Experimental Data.** It will be seen in Chart 1 that the 5 control animals began to show definite weight changes in from 30 to 50 days after they began eating the experimental diet and xerophthalmia developed, as indicated by a circle with a cross on it, after 45 to 75 days on the diet. Death occurred from 65 to 129 days after the diet was begun as indicated by a cross on the chart.

The animals that received a daily dose of 0.5 cc. of cottonseed oil with 2 units of vitamin A slowly resumed growth. This supplement was begun when depletion of vitamin A was evident, and it is indicated by an arrow on the chart. Rat 5 grew poorly and lost some weight near the end of the experiment. Rat 31 also lost weight and had a reappearance of xerophthalmia near the conclusion of the experiment.

Chart 1 also shows the effect of 2 units of vitamin A dissolved in a daily dose of 0.5 cc. of mineral oil begun after depletion was apparent by a cessation of growth. In this group of animals growth resumption was at least as good when mineral oil carries vitamin A, as when it is present in cottonseed oil. The growth of the animals following the administration of vitamin A in mineral oil, shows that they are able to extract the vitamin A from the mineral oil.

When this experiment was begun it was not known whether the experimental animals could remove any of the vitamin A from the mineral oil or whether they might be able to remove only a portion of it. Since 2 units of vitamin A are sufficient only for maintenance and not for normal growth, it seemed necessary to have comparative growth curves of rats on larger doses of vitamin A, both in an absorbable medium and in the unabsorbable mineral oil. Charts 2 and 3 represent the effect on growth of daily doses of 4 and 6 units of vitamin A in 0.5 cc. of cottonseed oil on rats previously depleted by a deficient diet compared with the effects on growth of daily doses of 4 and 6 units of vitamin A in 0.5 cc. of mineral oil on rats depleted of vitamin A. A small chart of the control animals is included for comparison. It is again apparent that rats can quantitatively extract the vitamin A from mineral oil if growth increases

are used as indices. Growth, during the administration of vitamin A in mineral oil, is as good as growth with vitamin A in cottonseed oil.

Chart 4 shows that 2 units of vitamin A daily give poorer growth after depletion than 4 units daily. There is no real difference in growth resumption on 4 and 6 units of vitamin A daily so that the optimum amount of vitamin A for good growth after depletion is no more than 4 units but is more than 2 units of our concentrate of fish liver oils. With the exception of one animal, Rat 28, that grew unusually well, the growth curves after depletion of vitamin A are as good, when a medium of unabsorbable mineral oil is used, as when an absorbable oil such as cottonseed oil is used.

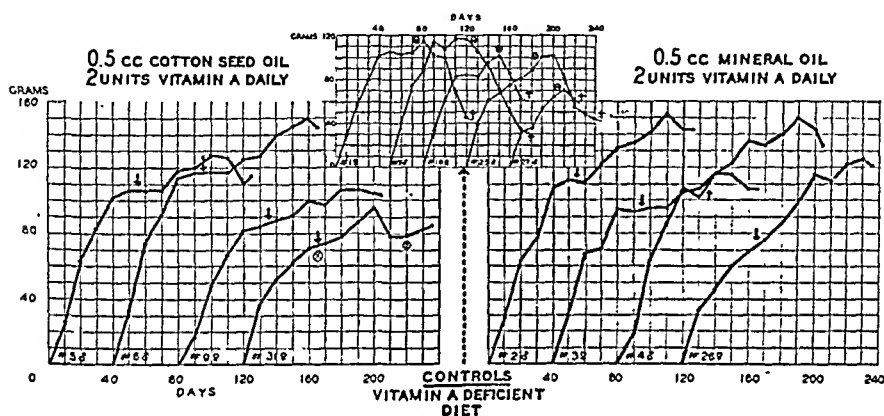


CHART 1.—GROWTH CURVES AND XEROPHTHALMIA.

The growth curves and time of development of xerophthalmia of the control animals on vitamin A depletion diets are illustrated in the smaller upper middle part of the chart. The left chart shows first the growth curves of animals on the depletion diets and then the effect of daily amounts of 0.5 cc. of cottonseed oil and 2 units of vitamin A begun when vitamin A depletion had occurred. The chart on the right illustrates the growth curves on another group of animals on the same depletion diets but differs in that mineral oil with 2 units of vitamin A were given in 0.5 cc. doses daily instead of cottonseed oil. ⊕, xerophthalmia; †, death; ↓, day when cottonseed oil with vitamin A or mineral with vitamin A was begun.

**Discussion.** From the experiments herein described it seems that one of the major objections to the use of mineral oil as a cathartic can be controlled by making a mixture of vitamin A and mineral oil, or by giving vitamin A with mineral oil. Although carotene would still be lost by its preferential solubility in mineral oil, enough vitamin A could be taken with or put in the mineral oil to give back to the body as much or more vitamin A than the mineral oil would remove as carotene from the food. This could be done by either taking enough fish liver oil with each dose of mineral oil to supply the daily requirement of vitamin A or by making a mixture of mineral oil that would have from 3000 to 6000 units of vitamin A in each average dose. The resulting mixture would have the advantage of being colorless, and could be made practically tasteless and odorless.

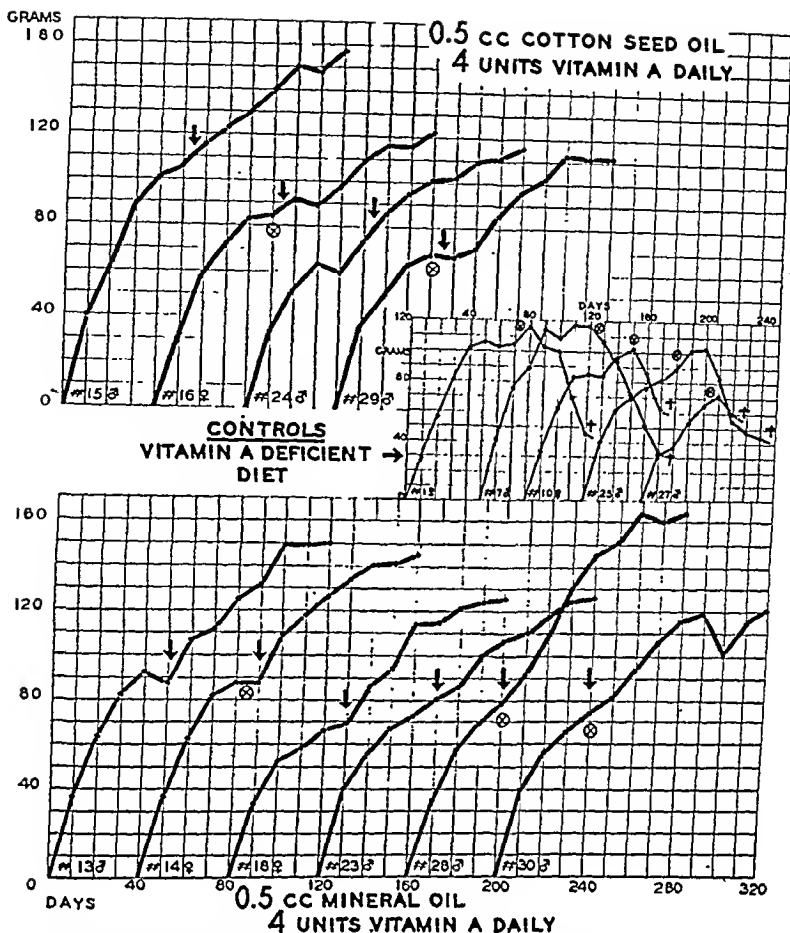


CHART 2.—The effect of 4 units of vitamin A. This was given daily in either 0.5 cc. of cottonseed oil or mineral oil on the growth of rats depleted of vitamin A by a vitamin A depletion diet. A small curve of the control rats on the depletion diet is inserted for comparison. ⊕, xerophthalmia; †, death; ↓, day when cottonseed oil with vitamin A or mineral oil with vitamin A was begun.

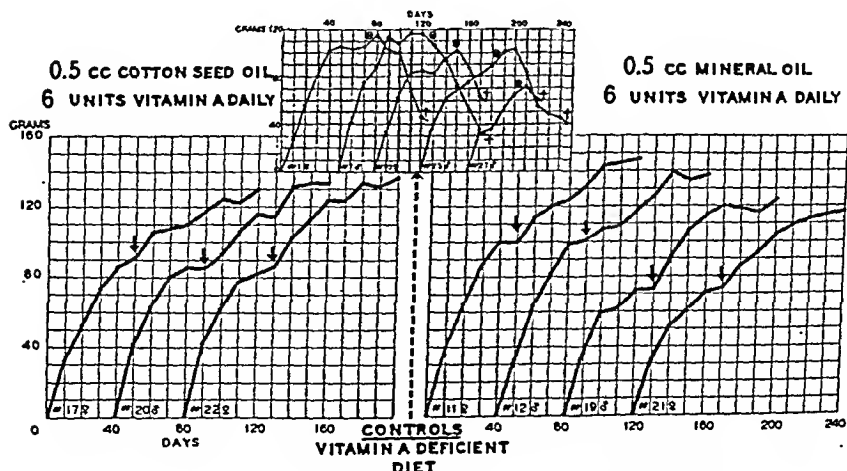


CHART 3.—The effect of 6 units of vitamin A. This was given daily in either 0.5 cc. of cottonseed oil or mineral oil on the growth of rats depleted of vitamin A by a vitamin A depletion diet. A small curve of the control rats on the depletion diet is inserted for comparison. ⊕, xerophthalmia; †, death; ↓, day when cottonseed oil with vitamin A or mineral oil with vitamin A was begun.

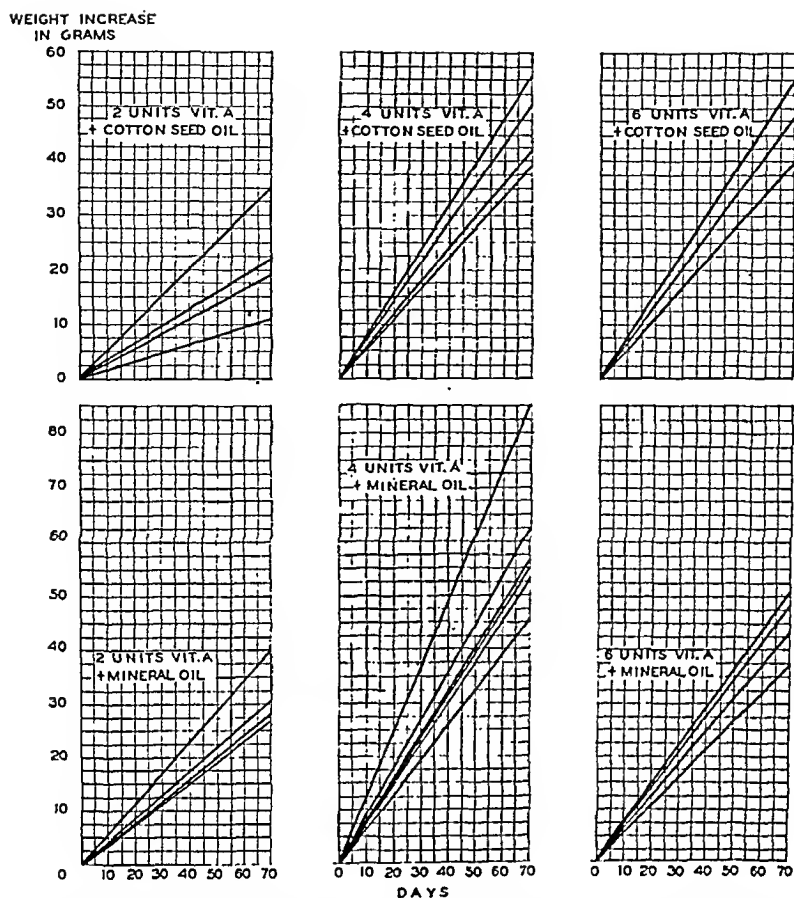


CHART 4.—Gain in weight following vitamin A. The relative gain in weight, during the 70 days which followed the depletion period when the animals received 2, 4 and 6 units of vitamin A dissolved in cottonseed oil compared to the gain in weight during the same period of the animals that received 2, 4 and 6 units of vitamin A dissolved in mineral oil.

**Conclusions.** 1. Three groups of rats, showing signs of vitamin A depletion, resumed as good growth on 2, 4, or 6 units of vitamin A in 0.5 cc. of mineral oil daily as rats receiving the same amount of vitamin A in 0.5 cc. of cottonseed oil daily.

2. Because of the preferential solubility of carotene in mineral oil, a sufficient amount of vitamin A should be taken with or dissolved in mineral oil whenever it is used as a cathartic or food substitute.

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## BOOK REVIEWS AND NOTICES

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THE ESSENTIALS OF MEDICAL TREATMENT. By DAVID MURRAY LYON, M.D., D.Sc.; F.R.C.P. ED., Professor of Clinical Medicine, The University, Edinburgh. Pp. 448; 19 illustrations. Edinburgh: Oliver & Boyd, 1939. Price, 15/-.

THIS volume was written as a guide for undergraduate and practitioner, because of the "comparative neglect of this subject" in undergraduate instruction. The book is well written and contains much and very excellent therapeutic advice. Its chief defect, however, lies in its brevity. For, in the attempt to cover the whole range of medical treatment within the limits of this small volume, the author has at times given scarcely the barest essentials. Although the book might be useful to the student for review purposes, it would not serve as a reference volume for the practitioner.

R. K.

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A HISTORY OF TROPICAL MEDICINE. Based on The Fitzpatrick Lectures delivered before the Royal College of Physicians of London 1937-38. (In two volumes.) By H. HAROLD SCOTT, C.M.G., M.D., F.R.C.P. LOND., D.P.H., D.T.M. and H. CAMB., F.R.S.E., Director, Bureau of Hygiene and Tropical Diseases; Member of the Colonial Advisory Medical Committee, etc. Pp. 1165; illustrated. Baltimore: The Williams & Wilkins Company, 1939. Price, \$12.50 per set.

THIS valuable work, based on the Fitzpatrick Lectures for 1937-1938, deals chiefly with somewhat more than a dozen diseases (malaria, blackwater fever, yellow fever, trypanosomiasis, leprosy, cholera, plague, the avitaminoses, and so on) that are generally associated with tropical countries. The author, of course, recognizes that "Tropical Medicine" is not an accurate term: it necessarily includes diseases that occur also in non-tropical regions but are less common there, and others that were once erroneously thought to be restricted to tropical zones. It is also noted that some diseases (cholera, plague, leprosy), now mostly confined to torrid zones for reasons not connected with temperature, were formerly widespread in temperate regions. Other diseases have not yet spread beyond warm climates because their vectors have not yet flourished elsewhere.

Dr. Scott views the disease situation in warm countries when they first came under European rule, then traces the improvements effected. The state of the navy and mercantile marine and the army is considered, and here as elsewhere the British Empire furnishes the bulk of the material. In the 139 pages devoted to malaria, for instance, Laveran, Grassi, Celli, the Italians and the Jesuits receive credit, to be sure, but the picture is mainly built on the basis of British studies and activities.

Two "tropical" poisons are considered: the Akee poisoning first seen on the Gold Coast, and Jamaica Ginger Paralysis (Jake Paralysis) first recognized in 1930 in this country. The rôle of the Suez and Panama Canals and of the Slave Trade in the spread of disease is described in 3 interesting chapters devoted to these subjects.

A final chapter gives 15 brief biographies from Bontius to Ronald Ross, though such pioneers as Pringle, Lind, Cooke and Thomas Trotter receive due notice in the text.

Nine pages of bibliography and 65 pages of index testify to the careful and authoritative nature of this production. It has value both for the medical historian and the thorough student of tropical medicine, and especially in its portrayal of the British contributions to the subject.

E. K.

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TREATMENT OF SOME COMMON DISEASES (Medical and Surgical). By Various Authors. Edited by T. ROWLAND HILL, M.D. (LOND.), M.R.C.P. (LOND.), Physician to the Southend General Hospital; Assistant Physician to the West End Hospital for Diseases of the Nervous System, etc. Pp. 398; 90 illustrations (several in color) and many Roentgen rays. Baltimore: The Williams & Wilkins Company, 1939. Price, \$5.00.

NOT a textbook, but a series of practical monographs on treatment by 21 members of the staff of the Southend General Hospital, London. The subjects discussed are angina pectoris, heart failure, pleurisy, bronchopulmonary suppuration, anemia, cerebral vascular disease, digestive disorders of infancy and childhood, prophylactic treatment by immunization, malignant disease of the pharynx, obstructive jaundice due to malignant disease, hemorrhage from the intestinal tract, enlargement of the prostate gland, infections of the face and neck, suppurative lesions about the knee joint, head injury, uterine hemorrhage, delayed labor, shock during anesthesia, pre-anesthetic medication, Roentgen rays in the treatment of malignant disease, injuries to the skin and mucous membranes in radiation therapy, moles, warts and angiomas, ocular complications of certain disorders of the skin, earache, dental caries and postoperative wound complications. The presentations are concise, but adequate. It is the type of book that general practitioners seem to value highly. There is, however, too much material that belongs strictly in the province of specialists (*e. g.*, cholecystenterostomy, prostatectomy, drainage of the knee joint, deep Roentgen therapy of tumors).

R. K.

#### THE MALARIAL THERAPY OF GENERAL PARALYSIS AND OTHER CONDITIONS.

By WILLIAM H. KUPPER, M.D., Formerly Resident Physician, Florida State Hospital and Special Physician Associated with the Station for Malarial Research, International Health Division of the Rockefeller Foundation, Tallahassee, Florida. Pp. 155 (lithoprinted); 8 illustrations. Ann Arbor: Edwards Brothers, Inc., 1939. Price, \$2.25.

THIS concise monograph tells of the fever therapy movement, mechanism of cure in malarial therapy of general paralysis, different malarial parasites, cure of the induced fever, malarial therapy in syphilitic manifestations other than general paralysis, comparison of malaria with other non-specific agents, the influence of natural and induced malaria upon early syphilis, and malarial therapy in dementia precox and other non-specific conditions. It is believed that the reticulo-endothelial system, and not the fever, is the important factor; at first, the functions of this system are impaired, but following the fever they are improved. Malarial fever is preferable to that induced through electrical machines. The Anopheline mosquito is the insect of choice. The Rockefeller Institute affiliation has an efficient insectary designed by Dr. Mark F. Boyd. From 30 or more wild, caged mosquitoes, the ova are collected; these, having hatched in 2 or 3 days, if supplied with suitable nourishment will ripen in some 30 days and, from the developed larvæ, the mosquitoes emerge; since the insects have not been infected, they are without danger to the technician who permits daily blood feedings from his arms and legs; their subsequent inoculation is tedious work. The difficulties of rearing the mosquitoes having been overcome, this method is preferable for institutions to the commonly used methods of direct inocula-



tion with malarial blood. Statistics from a large hospital show that previously, the number of paretics discharged as improved was 2.6 per cent, and the death rate was 62.1 per cent; of a group treated with malaria, 33.5 per cent were discharged, and only 20.9 per cent died. Of the other diseases where malarial therapy has been tried, gonorrhea has been most responsive. The bibliography covers 25 pages. N. Y.

**LIFE AND LETTERS OF DR. WILLIAM BEAUMONT.** By JESSE S. MYER, A.B., M.D., Late Associate in Medicine in Washington University, St. Louis. With an Introduction by SIR WILLIAM OSLER, Bt., M.D., F.R.S., Late Regius Professor of Medicine in Oxford University, England. Pp. 327; illustrated. St. Louis: The C. V. Mosby Company, 1939. Price, \$5.00.

THIS work first appeared in 1912 with a characteristic Introduction by Sir William Osler. It is now reprinted with a "Present-Day Appreciation" by Dr. A. C. Ivy, Professor of Physiology and Pharmacy at Northwestern University. In the interim the importance of Beaumont's work has become more thoroughly appreciated—societies have been named for him, "shrines" created, and in 1929 it was his portrait that was chosen to adorn the medal of the International Congress of Physiology. Anyone interested in Beaumont can hardly dispense with this authoritative statement.

E. K.

**LEE ON THE LEVEE (An Historical Novel).** By RALPH CANNON. Pp. 188. New York: The Saravah House, 1940. Price, \$2.50.

THIS pleasant novel about the young Robert E. Lee's engineering activities on the Mississippi has a special interest for medical readers in its portrayal of his friendship with the physiologist Beaumont, to whose experiments with St. Martin considerable space is here given.

E. K.

**THE NEWER NUTRITION IN PEDIATRIC PRACTICE.** By I. NEWTON KUGELMASS, B.S., M.A., M.D., Ph.D., Sc.D., Attending Pediatrician, Broad Street Hospital and Hecksher Institute, New York; Consulting Pediatrician, Lynn Memorial, Monmouth Memorial and Muhlenberg Hospitals, New Jersey, etc. Pp. 1155; 183 illustrations. Philadelphia: J. B. Lippincott Company, 1940. Price, \$10.00.

THIS volume covers the entire field of nutrition in health and disease during infancy and childhood. The author's major premise is stated in the preface—"an understanding of the normal functions of the body in relation to each of the fifty essential nutrients (22 amino acids, 12 vitamins and 13 minerals) is the only basis for individualizing nutrition at all ages, types of constitution and levels of body functioning."

While there is a valuable collection of physiologic and nutritional data and innumerable useful diet lists, the Reviewer feels that the author does not follow this premise in the presentation of his material. It is highly questionable whether the fifty essential nutrients elements are all essential; certainly, the exact value and need for many of the fifty in human nutrition are still unproved.

Most of the approved nutritional procedures and régimes of the pediatric period are adequately presented, but many enthusiastic and unreserved recommendations of the author are by no means unanimously accepted. To cite just one of many—the careful study of Senn on the use of the author's hydrating solution in newborn infants is certainly not in agreement with the author's statements.

M. R.

**ELMER AND ROSE PHYSICAL DIAGNOSIS.** Revised by HARRY WALKER, M.D., F.A.C.P., Associate Professor of Medicine, Medical College of Virginia, Richmond. Pp. 792; 295 illustrations. Eighth edition. St. Louis: The C. V. Mosby Company, 1940. Price, \$8.75.

DR. WALKER, in revising Dr. Elmer's revision of Dr. Rose's work, has definitely improved on previous editions, not only by weeding out useless material and including new developments in the field, but by a better arrangement of the subject matter. The book is primarily intended for teaching physical diagnosis to students, and for this purpose it is adequate. Its chief virtue lies in its viewpoint that "physical diagnosis" refers to the whole patient and not simply the examination of the thorax and its contents. As a reference work, however, it is too abbreviated. Thus there is no mention of physical signs due to foreign bodies in the air passages, or those occurring in bacterial endocarditis of the right side of the heart. An interesting innovation is pale-green paper instead of white. R. K.

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**PRINCIPLES OF ORTHOPEDIC SURGERY.** By JAMES WARREN SEVER, M.D., Assistant Professor of Orthopedic Surgery, Harvard Medical School; Orthopedic Surgeon, Children's Hospital, Boston; Associate Surgeon, Boston City Hospital, etc. Pp. 418; 221 illustrations. Third Edition. New York: The Macmillan Company, 1940. Price, \$3.25.

A CONCISE, well-written book. Clearly printed; amply illustrated with clear cuts; good margins and nicely bound in fabrikoid.

This book should prove of value to medical students and those practitioners desiring a fairly comprehensive but not detailed text. It cannot compete with the larger definitive works of Whiteman, Campbell or Steindler. It can however be recommended as an authoritative work of considerable value. G. W.

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**CYCLOPROPANE ANESTHESIA.** By BENJAMIN HOWARD ROBBINS, B.A., M.S., M.D., Associate Professor of Pharmacology, Vanderbilt University School of Medicine. Pp. 175; 40 illustrations. Baltimore: The Williams & Wilkins Company, 1940. Price, \$3.00.

THIS excellent little volume is one more witness to the fact that anesthesia is assuming a place of its own in the medical world. It shows the need for coöperative endeavor on the part of the chemist, physicist, physiologist, pharmacologist and surgeon in the search for the "perfect anesthetic."

The book outlines the physical and chemical characteristics of cyclopropane. It discusses, on the basis of recent investigation, many undertaken by the author himself, the effect of cyclopropane on circulation, respiration, the gastro-intestinal tract, blood and other body tissues. Physiological principles are invoked and suggestions made for the application of these in the clinic. One wonders if the value of cyclopropane in obstetrics has been unduly praised and the dangers from explosion minimized. R. D.

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**SYNOPSIS OF OBSTETRICS.** By JENNINGS C. LITZENBERG, M.D., F.A.C.S., Professor Emeritus of Obstetrics and Gynecology, University of Minnesota Medical School, Minneapolis. Pp. 394; 157 illustrations (5 in color). St. Louis: The C. V. Mosby Company, 1940. Price, \$4.50.

THE author has brought the wisdom gained from long years of clinical experience into the preparation of this synopsis. Brevity marks the text, and practically every paragraph states an obstetric axiom. Emphasis is lent to many points by having the text printed in heavier type or italics. The volume consists of 38 chapters which deal with the normal course of

labor and the puerperium as well as the pathology, complications, and surgery of the subject. It is an excellent and a concisely written general review of obstetrics in a convenient form which should provide means for a quick review of the subject for either practitioner or student.

P. W.

**DIABETES.** Practical Suggestions for Doctor and Patient. By EDWARD L. BORTZ, A.B., M.D., F.A.C.P., Associate Professor of Medicine, Graduate School of Medicine, University of Pennsylvania; Chief of Medical Service B, The Lankenau Hospital, Philadelphia, etc. With a Foreword by GEORGE MORRIS PIERSOL, B.S., M.D., F.A.C.P., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania. Pp. 296; 15 illustrations and 6 tables. Second Edition, revised and enlarged. Philadelphia: F. A. Davis Company, 1940. Price, \$2.50.

THE present edition of this manual has been enlarged and revised particularly in the section dealing with insulin. The use of protamine zinc insulin and crystalline insulin, together with the differences in hypoglycemic, symptoms induced by both of these in contrast to those of standard insulin, is discussed. The illustrations are well chosen. An excellent table on the differential diagnosis of various types of coma is again included.

Separate chapters by collaborators are devoted to diabetes in childhood, diabetic surgery, dental care, care of the feet, and dietary management. The use of special diabetic food is condemned. The recipes for common dishes would be more valuable if the amounts of carbohydrate, protein and fat were given. The table of food values includes the amounts of vitamins, iron, calcium and phosphorus. Inclusion of U-10 insulin and of the U-10—U-20 syringe is of dubious value; likewise confusion may result from "calories per square foot" and metabolic "rate per square meter" in the same paragraph on page 63.

For patients and practicing physicians this manual is an excellent ready reference.

M. B.

**A TEXTBOOK OF SURGERY.** By JOHN HOMANS, M.D., Clinical Professor of Surgery. Compiled from lectures and other writings of 23 members of the Surgical Department of the Harvard Medical School. With a Special Bibliographical Index. Pp. 1272; 530 illustrations by WILLARD C. SHEPARD. Springfield, Ill.: Charles C Thomas, 1940. Price, \$8.00.

THIS textbook, edited by Doctor Homans but compiled from the lectures and other writings of 23 members of the Surgical Department of the Harvard Medical School, has stood the test of time. First issued in 1931, it has been revised often enough and carefully enough to keep it well abreast of newer developments in physiology and surgery. While no textbook seems perfect, except perhaps to the author or authors, this one can be recommended without reservation as one which will fill the demands of the usual courses in surgery. The bibliographical index is particularly good, though text references to the bibliography might be of advantage. We shall hope for further revisions and additions to this valuable text as they are needed.

I. R.

**SEX AND LIFE. FORTY YEARS OF BIOLOGICAL AND MEDICAL EXPERIMENTS.** By EUGEN STEINACH, M.D., PH.D., Formerly Professor of Physiology at the University of Vienna. The scientific values adapted to the lay reader by JOSEF LOEBEL, M.D. Pp. 252; 67 illustrations (many in color). New York: The Viking Press, 1940. Price, \$3.75.

THIS book first discusses the age-long ideas of the relation between Sex and Life before any scientific knowledge of the hormonal aspects of the

gonads had been developed. It then proceeds to a discussion of the relationship of the sex organs to the nervous system and of physical and psychic sex characters. Realizing that the generative organs control physical and psychic sex manifestations, the author transferred his attention to the transplantation of sex glands in animals—the field that is most widely connected with his name. He believes that through such transplantations sex characteristics could be maintained in a state of maturity. The effects of deprivation, castration, vasoligation or surgical reactivation, in animals as well as in the human, are discussed. The subject of senescence in both male and female is considered from a standpoint of his reactivation experiments. The comparative effects in veterinary medicine are appended. He describes in detail the entire operation of vasoligation, the operation to which his name has been attached.

The book closes with a rather conservative presentation of the effects of both the male and female sex hormones. It represents the first personal presentation, aside from a few case reports, of the long years of physiologic and biologic studies of the sex glands by one of the pioneers in this field. It is important in that in its presentation it is freed from any of the distortions or exaggerations usually connected with this man's experiments.

P. W.

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THE PATHOLOGY OF INTERNAL DISEASES. By WILLIAM BOYD, M.D., LL.D., M.R.C.P., Ed., F.R.C.P., Lond., Dipl., Psych., F.R.S.C., Professor of Pathology and Bacteriology in the University of Toronto, Toronto; Formerly Professor of Pathology in the University of Manitoba, Winnipeg. Pp. 874; 353 illustrations and 4 colored plates. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, \$10.00.

EARLIER editions have caused this book to be recognized as one of the most valuable and readable in pathology, from the standpoint of general physicians, pathologists and medical students. In the preparation of the third edition, a great deal of revision was not necessary; but a number of subjects have been brought up to date, such as the pathogenesis of lobar pneumonia and hemorrhagic pancreatic necrosis, and the etiology of glomerulonephritis. New material has been added on the relation of the pituitary to diabetes, vitamin K deficiency, internal coronary hemorrhage and other subjects. There are a number of good new illustrations.

M. McC.

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THE MANAGEMENT OF OBSTETRIC DIFFICULTIES. By PAUL TITUS, M.D., Obstetrician and Gynecologist to The St. Margaret Memorial Hospital, Pittsburgh, Consulting Obstetrician and Gynecologist to the Pittsburgh City Homes and Hospital, Mayview, etc. Pp. 968; 368 illustrations, and 5 color plates. Second Edition. St. Louis: The C. V. Mosby Company, 1940. Price, \$10.00.

THE second edition of Titus' "Management of Obstetric Difficulties" has been revised to include some recent advances in various phases of the subject of obstetrics. Probably originally conceived as a book to meet the problems implied in its title, the volume really is a fine portrayal of practical clinical obstetrics. There are few situations which arise in obstetric practice for which a solution would be sought in vain in the text. Of particular note in the additions to this edition is a discussion of sulphanilamide in the infections of the reproductive cycle, although the author is conservative in the dosage suggested.

To obviate obstetric difficulties, he has given a thorough consideration of what Roentgen ray pelvimetry may signify in the diagnosis of disproportion.

Recent contributions on obstetric analgesia and anesthesia are well evaluated. There are many new illustrations which add much to the value of the book.

For the practicing obstetrician or the general practitioner without ready access to a consultant this book should continue to fulfill a definite need.

P. W.

**AN INTRODUCTION TO GASTRO-ENTEROLOGY.** Being the Third Edition of *The Mechanics of the Digestive Tract*. By WALTER C. ALVAREZ, Professor of Medicine, University of Minnesota, The Mayo Foundation, and a Senior Consultant in the Division of Medicine, The Mayo Clinic. Pp. 778; 186 illustrations. New York: Paul B. Hoeber, Inc., 1940. Price, \$10.00.

THIS book, being an amplification of the author's well-known work on "The Mechanics of the Digestive Tract," will be welcomed by all gastro-enterologists. It brings up to date, including much new material, a connected story of the recorded data and opinions regarding the physiology of the digestive tract and at the same time presents Alvarez' application of such fundamental knowledge to clinical medicine. Whether or not one agrees entirely with his theory of an intestinal gradient of activity, one must admit that it seems to explain many puzzling phenomena.

As always Alvarez' discussions are to the point, informative and stimulating. Because the book presents reasonable explanations for many obscure clinical phenomena it should appeal to all practitioners of medicine, and because of the thoroughness with which it covers the literature and of its extensive bibliography it should be in the hands of all investigators in the field of gastro-enterology.

J. N.

**FETAL AND NEONATAL DEATH.** A Survey of the Incidence, Etiology, and Anatomic Manifestations of the Conditions Producing Death of the Fetus in Utero and the Infant in the Early Days of Life. By EDITH L. POTTER, M.D., Ph.D., Instructor in the Department of Obstetrics and Gynecology, The University of Chicago; Pathologist at The Chicago Lying-in Hospital, and FRED L. ADAIR, M.D., Professor and Chairman of the Department of Obstetrics and Gynecology, The University of Chicago and The Chicago Lying-in Hospital. Pp. 207; 31 illustrations. Chicago: The University of Chicago Press, 1940. Price, \$1.50.

IN view of the increasing emphasis upon the conservation of human life, especially that of pregnant women and newborn infants, the present contribution is timely. In this small volume the authors have brought together pertinent facts regarding the following subject: 1, Birth rates, and those of stillbirths and infant deaths; 2, the characteristics of the normal fetus and infant; 3, a consideration of postmortem examinations; 4, a survey of the principal causes of fetal and infant death; 5, a chapter dealing with special pathology.

The authors note the declining birth rate in this country and the inadequacy of our statistics regarding the causes of stillbirth. Although they note a decline in the deaths occurring under one year of age, the deaths under one day of age have exhibited no significant change. Considerable space is devoted to the characteristics of the normal infant. This subject is important to the obstetrician as well as to the pathologist and the roentgenologist.

The volume as a whole was written for the purpose of showing some of the reasons for fetal and infant deaths and as a basis for further investigations. The authors, however, did not make any recommendations regarding the future, on the basis of their observations. The book will be a valuable asset to obstetricians, pathologists and others interested in infant death.

D. M.

## NEW BOOKS

- Diagnosis and Treatment of Head Injuries.* By SIDNEY W. GROSS, M.D., F.A.C.S., Attending Neurosurgeon, Beth Israel Hospital; Associate Neurosurgeon, Morrisania City Hospital; Adjunct Neurosurgeon, Mt. Sinai Hospital, etc., and WILLIAM EHRLICH, M.D., Associate Attending Neurosurgeon, Newark Beth Israel Hospital; Neurosurgeon, Barnett Memorial Hospital, Paterson, etc. Introduction by PERCIVAL BAILEY, M.D., Ph.D., Professor of Neurology and Neurosurgery, University of Illinois, Chicago. Pp. 275; 94 illustrations. New York: Paul B. Hoeber, Inc., 1940. Price, \$5.00.
- Cyclopropane Anesthesia.* By BENJAMIN HOWARD ROBBINS, B.A., M.S., M.D., Associate Professor of Pharmacology, Vanderbilt University School of Medicine. Pp. 175; 40 illustrations. Baltimore: The Williams & Wilkins Company, 1940. Price, \$3.00. (Review, p. 111)
- The Foot and Ankle. Their Injuries, Diseases, Deformities and Disabilities.* By PHILIP LEWIN, M.D., F.A.C.S., Associate Professor of Bone and Joint Surgery, Northwestern University Medical School; Professor of Orthopaedic Surgery, Post-Graduate Medical School of Cook County Hospital, etc. Pp. 620; 303 illustrations. Philadelphia: Lea & Febiger, 1940. Price, \$9.00.
- Convalescent Care.* Proceedings of the Conference Held Under the Auspices of the Committee on Public Health Relations of The New York Academy of Medicine, November 9 and 10, 1939. Pp. 261. New York: The New York Academy of Medicine, 1940.
- Obesity and Leanness.* By HUGO R. RONY, M.D., Formerly Associate in Medicine and Chief of Endocrine Clinic, Northwestern University School of Medicine, Chicago; Formerly Attending Physician, Cook County Hospital, Chicago, etc. Pp. 300; 32 illustrations. Philadelphia: Lea & Febiger, 1940. Price, \$3.75.
- Dynamics of Inflammation.* An Inquiry into the Mechanism of Infectious Processes. (Experimental Biology Monographs.) By VALY MENKIN, Department of Pathology, Harvard University Medical School. Pp. 244; 50 illustrations. New York: The Macmillan Company, 1940. Price, \$4.50.
- El Corazón y La Circulación en Los Hipertiroideos.* Consideraciones Sobre Fisiopatología, Clínica y Terapéuticas. By HÉCTOR GOTTA, Médico de la Primera Cátedra de Semiología y Clínica Propedéutica, Hospital Nacional de Clínicas. Pp. 104; 13 illustrations and 13 charts. Buenos Aires: "El Ateneo," 1938.
- Pathological Histology.* By ROBERTSON F. OGILVIE, M.D., F.R.C.P. (Edin.), Lecturer in Pathology, University of Edinburgh; Senior Pathologist, Royal Infirmary, Edinburgh; Pathologist, Deaconess Hospital, Edinburgh; Examiner in Pathology for the Triple Qualification. Foreword by A. MURRAY DRENNAN, M.D., F.R.C.P. (Edin.), Professor of Pathology, University of Edinburgh. Pp. 332; 220 photomicrographs in color by T. C. DODDS, F.R.P.S., F.I.B.P., Senior Technician, Pathology Department, University of Edinburgh. Baltimore: The Williams & Wilkins Company, 1940. Price, \$8.50.
- Cancer. A Manual for Practitioners.* The Committee on Publication: GEORGE W. HOLMES, M.D., Chairman, ERNEST M. DALAND, M.D. SHIELDS WARREN, M.D., CHANNING C. SIMMONS, M.D., Editor. Pp. 284. Boston: Department of Health, 1940.
- Chemistry and Medicine.* Papers Presented at the Fiftieth Anniversary of the Founding of the Medical School of the University of Minnesota. Edited by MAURICE B. VISSCHER, Professor of Physiology at the University of Minnesota. Pp. 296; illustrated. Minneapolis: The University of Minnesota Press, 1940. Price, \$4.50.

*Manual of Peripheral Vascular Disorders.* By DAVID W. KRAMER, M.D., F.A.C.P., Assistant Professor of Medicine, Jefferson Medical College; Assistant Physician and Chief Clinic Assistant, Vascular Clinic, Jefferson Hospital, etc. Pp. 448; 126 illustrations. Philadelphia: The Blakiston Company, 1940. Price, \$6.00.

*The Electrocardiogram in Congenital Cardiac Disease.* A Study of 109 Cases, 106 with Autopsy. By MAURICE A. SCHNITKER, B.Sc., M.D., Formerly Resident Physician, Peter Bent Brigham Hospital and Assistant in Medicine, Harvard University Medical School, Boston, etc. Pp. 147; illustrated. Cambridge: Harvard University Press, 1940. Price, \$3.00.

*The March of Medicine.* Edited by the Committee on Lecturers to the Laity of the New York Academy of Medicine, William C. White, Chairman. Pp. 168. New York: Columbia University Press, 1940. Price, \$2.00.

### NEW EDITIONS

*Principles of Orthopedic Surgery.* By JAMES WARREN SEVER, M.D., Assistant Professor of Orthopedic Surgery, Harvard Medical School; Orthopedic Surgeon, Children's Hospital, Boston; Associate Surgeon, Boston City Hospital, etc. Pp. 418; 221 illustrations. Third Edition. New York: The Macmillan Company, 1940. Price, \$3.25. (Review, p. 111)

*Clinical Parasitology.* By CHARLES FRANKLIN CRAIG, M.D., M.A. (Hon.), F.A.C.S., F.A.C.P., Colonel U. S. Army (Retired), D.S.M., Emeritus Professor of Tropical Medicine in the Tulane University of Louisiana, New Orleans, and ERNEST CARROLL FAUST, M.A., Ph.D., Professor of Parasitology in the Department of Tropical Medicine, Tulane University of Louisiana, New Orleans. Pp. 772; 244 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, \$8.50.

*A Textbook of Pathology.* By W. G. MACCALLUM, Professor of Pathology and Bacteriology, The Johns Hopkins University, Baltimore. Pp. 1302; 695 illustrations. Seventh Edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1940. Price, \$10.00.

For years this has been one of the best and most successful textbooks of pathology. The reasons for its success are the clearly written and readable text and the excellent illustrations. The point of view is different from that of comparable books: pathologic conditions are arranged according to etiology rather than according to organs. The present edition introduces a number of minor changes; for example, conditions due to viruses are brought up to date.

*The Compleat Pediatrician.* Practical, Diagnostic, Therapeutic, and Preventive Pediatrics. For the Use of Medical Students, Internes, General Practitioners, and Pediatricists. By WILBURT C. DAVISON, M.A., D.Sc., M.D., Professor of Pediatrics, Duke University School of Medicine; Pediatricist, Duke Hospital, etc. Pp. 269. Third Edition. Durham, N. C.: Duke University Press, 1940. Price, \$3.75.

Rewritten because of the many additions to pediatric knowledge of the past three years.

*A Manual of the Common Contagious Diseases.* By PHILIP MOEN STIMSON, A.B., M.D., Assistant Professor of Clinical Pediatrics, Cornell University Medical College; Visiting Physician, Willard Parker Hospital, etc. Pp. 463; 54 illustrations and 6 plates, 4 in color. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, \$4.00.

*Treatment by Manipulation.* By A. G. TIMBRELL FISHER, M.C., M.B., Ch.B., F.R.S.C. (Eng.), Co-Trustee and Member of Executive and Research Advisory Committees of Empire Rheumatism Council; Corresponding Member of the American Academy of Orthopedic Surgeons, etc. Pp. 255; 68 illustrations. Third Edition of "Manipulative Surgery." New York: Paul B. Hoeber, Inc., 1939. Price, \$3.75.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF  
JOHN H. MUSSER, M.D.

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

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### ANEMIA IN PREGNANCY.

INCREASING interest in recent years in the classification of the anemias in general has led to a more careful study of the blood in pregnant women. No attempt will be made here to review the subject historically. Reviews of the older literature are available in the reports of Pepper,<sup>55</sup> Bland, Goldstein and First,<sup>13a,b</sup> and in the more recent report of Evans.<sup>24</sup> Pepper aptly points out that much of the literature antedates the era of modern hematology and this, together with the incompleteness of case reports, makes interpretation of earlier work difficult and at times impossible. The reports only of the last several years will be detailed here, together with pertinent information of interest from earlier sources.

The pregnant woman undergoes many physiologic changes which affect profoundly the functions and reactions of the entire organism. Such changes in the blood would necessitate the establishment of physiologic standards for pregnancy if any differences from the non-pregnant state developed. Thus Bethell and his associates<sup>11</sup> have defined true anemia of pregnancy as a condition characterized by decrease in the red blood cells, hemoglobin, or both, below levels considered as physiologic for gestation. These standards and the physiologic changes necessitating their establishment will be discussed below.

There are a number of ways in which anemias in pregnancy have been classified. Osler,<sup>53</sup> in 1919, divided them into four groups, severe anemias, those due either to postpartum hemorrhage or sepsis, and postpartum anemia. Alder,<sup>3</sup> in 1924, grouped them either into anemias with pregnancy, such as chlorosis, congenital hemolytic jaundice, post-hemorrhagic anemia, and others, or anemias from pregnancy including "physiologic anemia" and the pernicious anemia of pregnancy. Evans<sup>24</sup> classifies them as: 1, deficiency anemias, either microcytic or macrocytic, as will become evident below; 2, as anemia of hemorrhage; 3, anemia of sepsis; 4, hemolytic anemia; and 5, anemia with pregnancy as a complicating factor. Smallwood<sup>61</sup> has published a similar classification. Other classifications incorporating red cell morphology are in use. The present discussion will be grouped under three general head-



ings: 1, the physiologic changes in the blood in pregnancy; 2, anemias produced by pregnancy; and 3, the anemias incidental to pregnancy, or rather the occurrence of pregnancy in anemic women.

**The Physiologic Changes in the Blood in Pregnancy.** These changes will be considered only from the standpoint of red blood cells and hemoglobin. For many years confusion reigned as to the presence or absence of a "physiologic anemia" of pregnancy. Not only was such a possibility both confirmed and denied but actual increases in the number of red blood cells were also reported. As far back as 1881 patients have been described as having an increase in plasma and the necessity of differentiating this dilution of cells, or hydremia, from true anemia was pointed out. Since then many observers<sup>24</sup> have worked on this problem and careful studies of the blood in normal pregnant women have shown reduction of red blood cells and hemoglobin values for most patients. Kühnel,<sup>38</sup> in 15 women, found reductions in the number of red blood cells as early as the eighth week, and progression until the sixteenth to twenty-second week, with a rise then at about the thirty-fourth week due to diuresis at that time. Hydremia is a likely explanation of the early changes and reliable methods<sup>21</sup> applied to the woman at intervals throughout pregnancy have shown increases in blood and plasma volume beginning in the first trimester and reaching by the thirteenth week 16 and 18% respectively. At term these figures are 23 and 25%. Hemoglobin and total cell volume increase but do not keep pace with the blood and plasma volume and the hemoglobin and red blood cell determinations per unit volume of blood are diminished. Others in recent years have definitely shown this physiologic change as well.<sup>57</sup> The change progresses until about the twenty-sixth week. Thomson and associates<sup>68</sup> found increases in plasma volume up until the ninth month. Oberst and Plass<sup>50</sup> and Feldman and his associates<sup>26</sup> reached similar conclusions. Strauss and Castle,<sup>66b</sup> in their examinations of the blood of 200 women in different months of pregnancy, and in a smaller group followed from month to month throughout pregnancy, found in general a steady decline in the erythrocyte count, with lowest counts usually at the end of the second trimester. These changes did not correlate with age or parity. A rapid gain of approximately 500,000 red blood cells per c.mm. took place within a week after parturition. Similar observations of a sudden postpartum increase of red blood cell count have been repeatedly reported.<sup>28</sup> The rapidity of the gain, it has been pointed out,<sup>66b</sup> is evidence that blood formation is not entirely responsible. Using the results of Keith, Rowntree and Geraghty,<sup>36</sup> that the average blood volume of women decreased 1100 cc. within 7 to 10 days postpartum, while blood loss was only about 300 cc., they calculated that the changes in red blood cell count postpartum, as determined by them, could be accounted for by change in blood volume, and conversely the decrease in red blood cell concentration observed in the first 6 months of pregnancy could be explained on the basis of increasing blood volume.

All do not agree that hydremia may account for all the changes seen. Some feel that actual anemia based on inadequate diet and gastrointestinal disturbances may possibly play a part, as may infection, which often causes anemia, already established, to become worse in

pregnancy.<sup>44</sup> Two theories of the older literature, which have very little supporting evidence, are that of hemolysis and toxic hemolysins from the fetus or placenta<sup>4,34</sup> and toxic inhibition of the bone marrow. None of these toxic factors has been proven to be factual.<sup>66b</sup> It is interesting to note that the fall in hemoglobin may be checked by the administration of iron<sup>11,71</sup> even when the hemoglobin rises quickly after delivery. Such evidence has so far apparently not been explained on the basis of hydremia.

In the face of the evidence on hand one cannot deny that the fall in hemoglobin and red blood cells in pregnancy is at least partially due to dilution which is fully established by approximately the twenty-sixth week and does not indicate anemia. There is a reluctance,<sup>24</sup> and rightly so, to calling this change anemia, because, since there is evidence that hemoglobin and red blood cells increase though not as rapidly as the plasma, there are likely more hemoglobin and red blood cells functioning in the blood stream than in the non-pregnant state. Caution must be used in the interpretation of such findings. Simple hydremia would be expected merely to dilute the cells which are normal in size and hemoglobin content.<sup>27</sup>

The problem of differentiation of these changes from true anemias occurring as clinical entities in pregnancy becomes evident. The question immediately arises as to how extensive these changes may be and what level of hemoglobin we may use below which we can disregard the possibility of hydremia in diagnosis and assume true anemia to be present. In other words, we must establish a level for hemoglobin and red blood cells considered physiologic for pregnancy and judge the presence of anemia upon those standards. As will become evident from remarks under *Microcytic Anemia*, below, careful selection of normal patients is necessary. Such a level is not definitely established. Dieckmann and Wegner<sup>21</sup> consider the level to be 10 gm. hemoglobin per 100 cc. blood. Watson<sup>70</sup> places it at a lower figure, 7.7 gm. hemoglobin (55% Sahli), and states that any patient with a hemoglobin level of 60% or less should be investigated and anemia ruled out. Bethell and his associates<sup>11</sup> set the figures at 10 gm. hemoglobin and 3,500,000 red blood cells.

**Anemias Produced by Pregnancy.** It is evident that in certain instances true anemia may be present with values close to or exceeding the above levels. Hence it is important that the blood of the pregnant woman be checked. Anemia is often not recognized, if mild and without symptoms, at a very time when it is simplest to treat. If unrecognized, it may possibly play a rôle in the development of complications of pregnancy. It is probably one of the most frequently overlooked complications itself and yet there are generally satisfactory means to combat it.<sup>44</sup>

Pregnancy may act in some way to produce anemias which have their counterpart outside pregnancy. Hemorrhage, infection, inadequate use of necessary dietary principles for proper hematopoiesis are a few examples of such conditions. Concerning the character and treatment of anemias resting upon such bases as infection and hemorrhage nothing more will be said here. The removal of the etiologic agent, general measures, the use of chemotherapy, and adequate iron

supplies, where indicated, are the same as in similar instances outside the pregnancy state.

*Microcytic Hypochromic Anemia.* The frequency of anemia in pregnancy points definitely to factors as causes which have a direct relationship to the gravid state. It is known that pregnancy exerts an increased demand upon the mother for dietary requisites and it is particularly true that unless these women are directed in dietary choice they may not increase their intake of food to meet the new requirements. Furthermore, the diet may have been borderline or inadequate before the onset of pregnancy. They may feel no apparent need for an increase in certain dietary factors and continue to ingest the diet previously taken, whether or not it is adequate for their old or new physiologic state. Vomiting of pregnancy, gastro-intestinal disturbances, and peculiar dietary desires may also account for the deficiency. Likewise, the pregnant woman may develop certain physiologic changes which make for a more difficult utilization of erythropoietic materials.

It is true that anemia is not uncommon in general in women of childbearing age, particularly in certain parts of the world. For example, in a study in Scotland,<sup>18</sup> anemia was found in 16% of adolescent women and 45% of adult women. These patients supposedly represented a cross-section of the poorest classes of the population of Aberdeen and nearby areas. They did not present themselves for medical examination because of symptoms of ill-health. Other figures<sup>46</sup> tend to confirm these findings in the British Isles but not consistently in the United States,<sup>45,52</sup> and suggest the importance of the economic status.

In pregnancy, anemia is very frequent, particularly the hypochromic variety.<sup>13a,29,30,43,53</sup> Reid and Mackintosh,<sup>56</sup> in another British report, determined the hemoglobin level in 1108 pregnant women and 10.2% gave a reading below 70% (Haldane). The anemia was always hypochromic and division of the women on the basis of income showed a higher incidence in the lower income group. Parity had little influence on the degree of anemia, and age, work outside the home, or abnormality in pregnancy had no recognizable influence. In Cape Town,<sup>43</sup> similar results have been found. The hemoglobin values were lower in multiparæ and were higher in Europeans with higher incomes, and higher than in the colored race, nearly all of whom had lower incomes. References on economic status by other authors are quoted.

In this country, Bland, Goldstein and First<sup>13a</sup> found definite anemia, with red blood cell counts below 3,500,000 in one-half of 200 ward patients, while only about one-fourth (26%) of 100 private patients showed the same reduction. Hemoglobin values below 74% occurred in 82 and 62% of the patients, respectively. No relationship to parity, age, or blood pressure was evident and such possible etiologic factors as ill-health, foci of infection, toxemia, and syphilis were investigated but the extent of their influence was not sufficient to be determined. It was noted that in 34 of 48 women (71%) with red blood cell counts below 3,500,000 in the last trimester, rapid recovery took place post-partum. While hydremia played a part in these instances, and while anemia occurred in both groups, the distinct differences in the two economic groups is apparent. In another study these same authors<sup>13b</sup>

found in 1000 patients examined at various periods of gestation that 47.4% gave evidence of distinct reduction in red blood cells below 3,500,000 and 58.6% reductions in hemoglobin values to 70% (Dare) or less.

Greene<sup>30</sup> studied 229 white and 267 colored pregnant women. Hemoglobin values averaged 67 and 62.6%, respectively. About 75% of the white and 85% of the colored women had hypochromic anemia in the last 2 months of pregnancy. The anemias were reactive to iron. The differences in the two economic groups were again evident, although both groups had a high incidence of anemia. In another study<sup>15</sup> of 404 negro women, dietary deficiencies were found but were not considered wholly responsible for the anemia present. Labate<sup>39a</sup> found anemia in 48% of 881 patients in labor, 71% of whom had received no iron during the prenatal period. He believes that adequate diet is not enough to prevent anemia in pregnancy. Watson<sup>70</sup> found in 500 pregnant women hemoglobin values between 55 and 75% (Sahli) in 81%.

Despite the fact that all these series have not used comparable hemoglobin levels for estimation of anemia and have not considered the physiologic standards of the gestation period, many have, but if one definitely considers such levels the incidence of anemia is still high, as can be seen from some of the statistics given. Adair *et al.*<sup>2</sup> found 63.2% of pregnant women apparently anemic on non-pregnant standards and only 11.6% on standards of 10 gm. hemoglobin and 3,360,000 red blood cells. These results are low compared to those above and to those of Bethell,<sup>10</sup> who found 70% of 66 pregnant subjects with blood values too low to be accounted for on hydremia alone.

The influences of economic status are evident in all reports in which comparison of such groups has been made. It is significant that in 45 patients reported by Davies and Shelley<sup>19</sup> without anemia in pregnancy, 42 had a satisfactory dietary history. Dietary influences are bound up closely with economic conditions. Bethell *et al.*,<sup>11</sup> in finding true anemia in 54% of 158 clinic patients, state that it results most often from deficiency or impaired utilization of iron and also inadequate protein intake, the latter not responding to iron therapy alone. This group will be discussed further under *Macrocytic Anemia*. Strauss and Castle<sup>66b</sup> found that the type of dietary deficiency, such as low-protein and iron intake, was the same as that noted in other patients with hypochromic microcytic anemia.

That anemia occurs in all groups regardless of economic status indicates other possible factors. One of these appears to be the function of the gastro-intestinal tract. It is significant that in the observations of Strauss and Castle<sup>66b</sup> no appreciable anemia occurred in patients with a normal intake of food and also a normal gastric acidity. That hypochromic microcytic anemia may occur in non-pregnant women taking an amount of iron usually considered adequate, when there is a reduction in or absence of free hydrochloric acid in the stomach, is well known, has been emphasized many times and need not be repeated here. This factor appears at times to be important in pregnancy. It has been shown, for example,<sup>66b</sup> that when patients take comparable diets the hemoglobin loss in pregnancy varies with the gastric acidity.

Likewise, gastric analyses on 24 women in one study<sup>66a</sup> showed that 75 % of the patients did not secrete normal amounts of free hydrochloric acid or pepsin during more than one-half the period of pregnancy. Another study,<sup>39b</sup> however, does not give such nicely correlated results. In 56 women, 52 of whom were in the last trimester, normal acidity was found in 42 (75 %), hypochlorhydria in 9 (16 %) and achlorhydria in 5 (9 %). Labate does not believe a precise correlation is to be made between hypoacidity and anemia but that it may accentuate anemia from other factors. Davies and Shelley<sup>19</sup> found gastric secretion was usually normal when anemia was absent in pregnancy and that reductions in acidity were temporary. Of some interest is a study<sup>14</sup> on gastrectomized dogs. In 5 dogs in 15 pregnancies, marked to severe anemia occurred 11 times. Only once did anemia develop in 12 normal dogs in 12 pregnancies.

Also important in the production of anemia appears to be the fact that despite any deficiency in hematopoietic materials, the fetus continues to exert demands at the expense of the mother.<sup>66c</sup> It is rare that the infant is born anemic. In those rare instances where anemia of the newborn does occur, the mother is not necessarily anemic.<sup>31</sup> Even with anemic mothers, the red blood cell counts and hemoglobin of the infants are normal for that period of life.<sup>66c</sup> In fact, maternal anemia has been reported as associated with greater fetal polycythemia,<sup>29</sup> although such infants may develop anemia in the first year. The demand on the mother by the fetus for essentials of hematopoiesis has been likened to a chronic blood loss from other causes and represents a drain on the mother, especially in the latter part of pregnancy. The iron stores for the fetus must come either from the iron stores of the mother or from her food.<sup>32</sup> There are said to be 500 mg. of iron in the average fetus. Heath and Patek<sup>32</sup> state that if 10 % reduction in hemoglobin results from hydremia which may account for hemoglobin levels to about 70 %, a further reduction of 20 % due to demands of the fetus for iron would reduce the hemoglobin to 50 %, assuming no stores nor food source in the mother. With inadequate intake of iron, one may see that reduction of hemoglobin from fetal demands is likely and that repeated pregnancies, especially if frequent, might produce iron deficiency and anemia. Others, however, do not emphasize the fetal demands. The total additional requirement of iron incident to pregnancy has sometimes been given at lower figures than those stated above, about 250 mg.,<sup>11</sup> an amount in 500 cc. of blood. Nevertheless, infants from anemic mothers during the first year may develop moderate to severe anemia which may be prevented by administering iron to the mother during pregnancy, or corrected by a like procedure on the infant.<sup>46</sup> Such anemias appear to result from deficient storage of iron by the fetus because of a deficient maternal supply. Experiments on rats<sup>6</sup> bear out this contention.

Strauss and Castle<sup>66b</sup> found that anemia in pregnant women differed in no distinctive way from that outside pregnancy. Whether or not dietary deficiency results from inadequate intake or increased demands, it eventuates in the same pictures. To quote, "In short, then, in pregnancy the combination of the loss of blood building materials to the body, the lowering of the gastric acidity, and, in many cases, the

alteration of the diet of the patient, produces anemia by the same mechanisms that produce similar types of anemia in the non-pregnant individual."

The therapeutic requirements are clear so that the use of an adequate diet, iron, dilute hydrochloric acid, and other procedures, as in idiopathic microcytic anemia, is indicated.

*Macrocytic Anemia of Pregnancy.* True Addisonian pernicious anemia appears to be rare in pregnancy. However, the association of pernicious anemia with pregnancy had early beginnings. Many of Biermer's cases were in pregnant women.<sup>55</sup> In the earlier literature, lively discussion took place as to the rôle of pregnancy in pernicious anemia. At that time, however, diagnostic criteria were not as rigid as at present and the validity of many older reports must be looked upon with great suspicion. Any grave and severe anemia may have been called pernicious.

Macrocytic hyperchromic anemia of the pernicious type occurs with varying frequency in pregnant women.<sup>9</sup> Evans,<sup>25</sup> in England, did not find one instance of severe anemia in records of over 4000 pregnancies in the years, 1926-27. Richter, Meyer, and Bennett,<sup>57</sup> in this country, found no case in a year's survey of a service averaging 400 to 500 deliveries per month. However, Stevenson,<sup>64</sup> in Glasgow, found 30 patients in 6 years and Abramson,<sup>1</sup> in Sweden, 9 patients from 1933 to 1937. The incidence in relationship to deliveries is not stated. In general, frequency in temperate climates is said to be 1 in 10,000. Mays<sup>47</sup> found 4 in 9000 deliveries in Louisiana. In a report in 1939, Ritter and Crocker<sup>58</sup> state that only 1 case induced by pregnancy has been observed on the maternity service of the Philadelphia General Hospital. Strauss and Castle,<sup>66c</sup> in a study of 36 severe anemias of pregnancy, found 30 of the microcytic and 6 of the macrocytic type. The high incidence in India will be discussed below.

Clinically, the anemia tends to develop in the third trimester. Onset may be sudden or gradual. It may be discovered in the puerperium when starting in the last month of pregnancy and it has been called puerperal anemia by some.<sup>8</sup> Color indices are above 1, platelets and leukocytes are normal or diminished in numbers, mean corpuscular volume is increased, the blood picture in general simulating that seen in typical Addisonian pernicious anemia.<sup>66c</sup> Unlike true pernicious anemia, there is no relapse with omission of specific therapy following delivery, and achylia gastrica is not uniformly present. The gastric acidity varies. It may be normal, reduced, or free hydrochloric acid may be absent following histamine stimulation. In 2 of Strauss and Castle's 6 patients<sup>66c</sup> achylia was present. Two years later 1 of these women had normal gastric acidity and a subsequent pregnancy was not accompanied by macrocytic anemia, although hypoacidity occurred. Differential diagnosis includes the same diseases as pernicious anemia outside of pregnancy and includes thyroid disease, toxemia of pregnancy, endocarditis, sepsis, and other simulating conditions.<sup>67</sup>

The anemia has been attributed to various causes, especially in the older literature. These are reviewed by Studdiford.<sup>67</sup> The efficacy of brewers' yeast, particularly in reports from India, suggests an absence from the diet of the extrinsic factor of Castle. Castle's own observa-

tions suggest that it may be due to a deficiency state resulting either from a lack of extrinsic factor in the diet or from a lack of intrinsic factor in the gastric juice. Others have supported the latter view in certain instances.<sup>51</sup> The lack of intrinsic factor appears to be a temporary one, with return following delivery.

Liver preparations would be efficacious in the treatment in either instance and with adequate treatment by this means the old mortality rates of 40 to 70%<sup>4</sup> have been reduced until, with early recognition and treatment, almost all should recover. Transfusion is important in those seriously ill until response to liver therapy occurs. Termination of the pregnancy is not necessary. At times factors producing hypochromic anemia may also be present and then iron preparations are also indicated.

Bethell's group<sup>11</sup> has found in the mild anemias of many pregnant women a blood picture of reduced red cells with slightly elevated mean corpuscular volumes and color indices. This they ascribe to a nutritional basis, probably a lack of adequate dietary protein and suggest that when it is more severe it is probably the pernicious anemia of pregnancy. Elsom and Sample<sup>23</sup> also have investigated macrocytic anemia in pregnancy resembling pernicious anemia, and, like Bethell, have related it to dietary factors. The temporary nature of the disease, as stated above, suggests some type of temporary deficiency. The report of Strauss and Castle referred to above describes patients on poor diets late in pregnancy but did not indicate any possible single specific deficiency other than general statements concerning extrinsic factor. Elsom and Sample put 8 pregnant women on diets supplemented for adequacy in everything but vitamin B complex. Macrocytosis, increased mean cell volume and hemoglobin, reticulocytosis, along with other changes seen in pernicious anemia, sprue, and tropical macrocytic anemia occurred. Gastric acidity was not changed. The changes were greatest at the time the diet became theoretically inadequate in vitamin B. Administration of brewers' yeast or liver extract relieved all the characteristic changes and there was no significant difference in the effectiveness of these 2 therapeutic agents.

While Elsom tried to relate these changes to vitamin B, Bethell tried to relate similar changes to protein intake. Both reports indicate an anemia which could be the forerunner of a more severe macrocytic anemia as seen in pregnancy and emphasize the possibility of an extrinsic cause of a pernicious anemia of pregnancy as well as the possible temporary derangement in production of intrinsic factor.

There is little information concerning any relationship between macrocytic anemia of pregnancy and the blood picture of the newborn.<sup>58</sup> Without treatment of the mother, the infant's blood picture may be normal. The normal fetal blood picture, interestingly enough, resembles that of pernicious anemia subjected to effective continuous and potent stimulus to blood formation.<sup>72</sup> Ritter and Crocker<sup>58</sup> report anemia of the newborn in an infant born of a mother with macrocytic anemia. They believe that the anemia of both the mother and infant was due to dietary deficiency.

Particular mention must be made of the macrocytic anemia of pregnancy in India. Its incidence there is approximately 300 times the

European and American estimates, and good therapeutic results have been reported by Wills and others in the use of brewers' yeast, again leading to the possibility, as in Elsom's, Bethell's, and Strauss and Castle's reports, of dietary factors in the etiology of the clinical picture. For the work of Wills and others on tropical macrocytic anemia, and the relationship of brewers' yeast, liver, and other therapeutic agents to this type of anemia, the reader is referred to recent Indian reports.<sup>16a,17,49</sup>

The amazing number of cases in India has led to considerable study of the patients in that country. Most interesting is the recent report of Chatterjee<sup>16a,b</sup> who has reviewed some of the striking findings in these patients. It is apparently one of the commonest anemia syndromes in India, occurs seasonally with highest incidence in September, and affects all religions and races. Early in pregnancy it starts as a mild normocytic anemia (which may be hydremia) and passes through the microcytic to a severe macrocytic stage. It is observed only in pregnant women. There is free hydrochloric acid in the stomach, and bilirubin of the blood, icterus index, and red blood cell fragility are normal. The Van den Bergh reaction is negative and urobilinogen is absent from the urine, factors against an hemolytic origin. Reversal of the albumin globulin ratio of the blood has been observed and anasarca is common. Blood cholesterol falls markedly. Iron therapy is of value in the first and second stages with normocytic or microcytic cells. A third stage with microcytic or normocytic but hyperchromic cells reacts to liver therapy. In the fourth stage, with hyperchromic macrocytic anemia, transfusion alone is of help, but cholesterol therapy may be of some benefit.

The concept one gains from the stages and development of this anemia brings to mind the possibility of a clinical entity distinct and different from the pregnancy anemias seen in the Americas and Europe. However, the stages through which the patients pass resemble closely the effects of hydremia and the microcytic hypochromic anemia usually seen in pregnancy changing later into a macrocytic anemia, as seen in this country, but the lack of response to liver, reported in the fourth stage, is unexplained upon such a basis. The Reviewer, having never seen such patients, feels incompetent to interpret the findings.

*Hemolytic Anemia.* There is little evidence to support the possibility of an hemolytic factor, coming from the placenta or elsewhere, and responsible for hemolytic anemia in pregnancy. In the older literature Hofbauer<sup>34</sup> postulated an hemolysin produced in the chorion as the cause of maternal blood destruction in early pregnancy, a theory favored by the increased iron content of the urine of pregnant women. The theory was advanced to explain the "physiologic anemia."

Pregnancy may occur during the course of certain hemolytic anemias, which will be considered below. However, there are those<sup>24</sup> who believe that certain cases reported from time to time may be hemolytic and have the characteristics of Lederer's anemia. Lederer's anemia has been reported in the puerperium.<sup>22</sup> This type of anemia responds dramatically to blood transfusion, a procedure of temporary benefit only in the other types of anemia seen in pregnancy. In several reported cases<sup>35,40a</sup> there has been such a response to transfusion. Such evidence is, however, quite unsatisfactory in classifying these



patients and if the diagnoses were established there would still remain the problem of determining whether such anemias are incidental to or definitely related to pregnancy.

**Anemias Incidental to Pregnancy.** The possibility exists of pregnancy occurring in women with any type of anemia seen in the childbearing age; for example, anemia of blood loss, acute or chronic, infection, nephritis, leukemia, syphilis, true Addisonian pernicious anemia, and others. Hence, we may find, associated with pregnancy, any type of anemia occurring in the childbearing age outside of pregnancy and it may develop before or during the course of the pregnancy. There are, however, certain factors which tend to prevent the occurrence of pregnancy in anemic women. Anemia, of and by itself, is a commonly known cause of sterility and abortion.<sup>20,48,69</sup> Meaker states that "Anemia has a striking effect; even the milder grades produce considerable depressions of spermatogenesis and presumably of oögenesis." There is, as well, at least one anemia which appears to have an added effect in producing sterility, namely sickle-cell anemia.

**Sickle-cell Anemia.** This condition, confined almost exclusively to the colored race, represents most likely a congenital defect in red blood cell formation associated with considerable numbers of sickle-shaped red blood cells, and characterized clinically by anemia, bouts of abdominal pain with gastro-intestinal symptoms, cardiac changes, and leg ulcers. In the active phases of the disease pregnancy is a rarity. In 1934, Lash<sup>41</sup> found only 2 cases in the literature and reported another. Richter, Meyer and Bennett<sup>57</sup> observed a patient with sickle-cell anemia who delivered a live term baby. In 1936, Killingsworth and Wallace,<sup>37</sup> in a general study of sickle-cell anemia (sickle-cell trait), mentioned a patient with active sickle-cell anemia in the fourth month of pregnancy. In the same year Sharp and Schleicher<sup>60</sup> reported a patient with active disease followed through pregnancy. In 1937, 2 additional reports appeared, 1 by Lewis<sup>42</sup> and 1 by Sodeman and Burch.<sup>63</sup> Both stress the possibility that pregnancy may activate the latent disease. Page and Sifton<sup>54</sup> just recently reported 2 cases of sickle-cell anemia and again discuss the possibility of exacerbation of the disease by pregnancy. Lewis stressed the disease as a possible cause of abortions. Sodeman and Burch emphasized also the effects on fertility. In only 4 reported patients has a live full-term baby resulted.

The exact mechanism by which active sickle-cell anemia may cause sterility is not clear. Anemia itself is a cause of sterility and abortion, as mentioned above. Because of the unsatisfactory methods of treatment of sickle-cell anemia the presence of anemia for long periods of time, even through the adolescent period into adult life, may have a profound effect upon the reproductive functions. Then, too, the disease itself, aside from the mere presence of anemia, may affect in some unknown manner the reproductive function.

**Splenic Anemia.** Those anemias associated with splenomegaly which are generally included under the vague term "splenic anemia" are sometimes complicated by pregnancy. The reported cases have been reviewed by Serbin.<sup>59</sup> Allen's report<sup>5</sup> of 2 cases in 1924 recorded sudden death during delivery in 1 patient and survival of the second. The latter patient was treated by Roentgen radiation and in a second

pregnancy therapeutic abortion was done followed by sterilization and later by splenectomy. There was no liver involvement. Other similar patients have been reported,<sup>7,12,33,40b,59</sup> 1<sup>62</sup> with spontaneous rupture of the spleen at the third month, splenectomy performed, and term delivery. Progression of the anemia has occurred. Splenectomy during gestation, as in the case cited above, has been done in other patients<sup>33</sup> with term delivery. In some instances<sup>7,40b</sup> splenectomy has been done following termination of the pregnancy.

In general, pregnancy has aggravated the syndrome, although the reverse does not seem to be true.<sup>59</sup> Serbin emphasizes the use of both medical and surgical measures if the pregnancy is to terminate successfully with improvement of the patient's state. Preliminary medical therapy, with transfusion followed by splenectomy, seems indicated. Transfusion and splenectomy are important procedures, but when the condition is severely aggravated by pregnancy, even radical treatment may fail. Roentgen ray over the spleen, especially its intensive use, is not recommended during pregnancy.

As far as diagnostic aid is concerned, the statement is made that in normal pregnancy the spleen does not undergo any appreciable hypertrophy; enlargement during pregnancy is usually due to preëxisting disease.<sup>59</sup> A moderately enlarged spleen, up to 800 gm., may not disturb pregnancy. Up to 1000 gm. or more, some embarrassment is likely to occur because of encroachment on the space required by the growing uterus.

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## PEDIATRICS

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## HEART DISEASE IN CHILDREN.

IN the last two decades a striking advance in the cardiology of adults has taken place in the knowledge of the involvement of the coronary arteries and the resulting changes in the myocardium to the extent that the subject as taught 20 years or more ago has come to be inadequate in considering heart disease in adults today. While no such radical changes have occurred in cardiology of childhood, still there are many contributions to be found in the current literature, and some of these tend to alter the concepts of the pathology, treatment and prognosis of these conditions. It is timely to analyze these contributions and evaluate the changes which we should make in our study and treatment of these conditions.

Heart disease in childhood should be divided into two main headings,

congenital and acquired. The congenital lesions are mainly developmental although some occur as the result of disease in the mother. Dry<sup>9</sup> reminded us that the developing mammalian heart assumes functional activity at a very early stage of gestation. A study of the embryology and comparative anatomy of the heart is essential to an understanding of the cause and mechanism of human congenital cardiac anomalies. From the simple tube-like structures septal formations divide the auricle, the ventricle, the bulbus cordis and the common aorta or truncus arteriosus each into two sections. Next there is torsion of the cardiac tube followed by development of the bulbus cordis, incorporation of the sinus venosus into the right auricle, the evolution of the aortic arches, some becoming obliterated, while others become the permanent arch, pulmonary vessels and their branches. Finally there is closure of fetal channels after birth. Associated with each of these processes anomalous developments may occur and congenital cardiac lesions may be classified accordingly. The author's classification of congenital lesions does not differ materially from Maude Abbott's and others found in textbooks on the subject.

Along somewhat similar lines Bredt<sup>5</sup> attempted to evaluate the embryogenesis of certain maldevelopments in the light of their morphology and of current, but often controversial, theories. In his presentation of hearts with two or more anomalies, he has considered whether such multiple malformations were a necessary result of some primary failure of development in the sense that a septal defect may be secondary to, or compensatory to, stenosis of an ostium, or whether the multiple maldevelopments may be brought about by a factor acting independently on different parts of the developing organ. In another section he dealt with atresias and stenoses of the cardiac cavities and the ostia. In the discussion of persistent truncus arteriosus communis, he expressed the belief that when the trunk had a valve of three rather than four segments the anomaly was the result of suppression of the pulmonary artery or aorta and not simple persistence of an originally single truncus arteriosus. In another section he described some unusual auricular defects, such as an unusual defect of the septum, congenital bands of the interior of the auricles and atresia of the mouth of the coronary sinus. In the final section he presented failures of development of the coronary arterial system.

In discussing the progress in the recognition of congenital heart disease, McGinn and White<sup>26</sup> stated that in 7500 postmortem examinations performed at the Massachusetts General Hospital in the last 40 years, congenital heart disease was found 67 times (an incidence of 0.9%). Of the 67 patients with congenital heart disease, 21 were under 1 year of age. Of the 7500 autopsies, 3400 were made in the last 15 years, and in this group the incidence of congenital heart disease was 1.2%. The most common congenital defect in the latter group was patency of the ductus arteriosus, which occurred alone in 4 cases and in combination in 5 cases. One of the cases with a patent ductus arteriosus also had coarctation of the aorta. In 4 hearts there were interventricular septal defects, and in 2 others the condition was complicated by pulmonary stenosis, dextroposition of the aorta and enlargement of the right ventricle, comprising the tetralogy of Fallot. A correct clinical diagnosis

had been made 7 times, in 4 adults and in 3 infants under 1 year of age. In 5 other persons, including an infant, the condition was suspected and the correct diagnosis had been entered on the record. In 3 patients congenital heart disease was diagnosed, but the anatomic defect was not noted. One of these had a cor biloculare. In another the condition was diagnosed wrong as to the congenital structural defect. In the remaining 25 patients, including 4 infants, congenital heart disease was entirely unsuspected.

Ash, Wolman and Bromer<sup>1</sup> pointed out that great difficulties attend the clinical identification of congenital heart defects during infancy. Widely different and entirely unrelated lesions may present similar murmurs or no murmurs and may give rise to identical roentgenologic configurations. The electrocardiograms showed no constant change except in the mirror picture dextrocardia. An enlarged thymus gland, a cluster of enlarged mediastinal lymph nodes, pulmonary atelectasis or pneumonia can confuse the interpretation of cardiac contour and position. They felt that by a correlation of the various findings a correct clinical diagnosis was often possible, although too much success should not be expected in the neonatal period, during which complicated abnormalities are frequent. They indicated that cyanosis is not a good criterion for differentiation of the various groups of lesions in infancy. It may be absent or delayed in the presence of lesions associated with venous-arterial shunt. Intermittent attacks may herald the presence of such a condition or may be merely transient phenomena associated with conditions in the "cyanosc tardive" group. When transient attacks of cyanosis are produced by permanent shunt of unoxygenated blood into the peripheral circulation, careful scrutiny of the lips and the nail beds will often detect a slight tint of blueness between attacks. On the other hand, patients with "delayed cyanotic" lesions are customarily entirely free from cyanosis between attacks. Progressive cyanosis beginning in the first weeks of life should be interpreted as indicating a lesion with permanent venous-arterial shunt. Polycythemia may be an indicator of venous-arterial shunting of blood even when cyanosis is not apparent. Anemia resulting from infection or nutritional inadequacies may modify preëxistent polycythemia.

Heart murmurs in newborn infants were studied by Lyon, Rauh and Stirling.<sup>24</sup> They found murmurs in 147 infants of a series of 7637 newborn infants who were examined during the first week of life (an incidence of 1.9%). In considering etiologic factors, sex, the month of birth, the birth weight, and the occurrence of syphilis in the mother seemed to play no part in the incidence of the murmurs. Of this group of 147 infants, 92 were followed later in life; 4 had died and heart disease was found in the autopsies of 2 of these infants; 14 had persistent systolic murmurs which were considered to represent some form of congenital cardiac lesion. Of the 74 remaining, 71 were entirely well without any clinical evidence of heart disease and 3 had functional murmurs or extrasystoles. The writers believed that in the period of readjustment of circulation during the first few weeks of life, patencies of the foramen ovale and of the ductus arteriosus usually do not produce clinical cardiac murmurs and that many other congenital anomalies of the heart do not cause murmurs during the neonatal period.

An unusual case was reported by Ladd.<sup>23</sup> In a full term baby, delivered normally, it was noted that there was cyanosis when feeding was attempted and the infant choked and regurgitated. This difficulty was more marked with breast feeding than with artificial feeding. Diaphragmatic hernia was suspected and confirmed by Roentgen studies. At the age of 2 years the baby was hospitalized for operation. Above the opening in the diaphragm in the thoracic cavity there was found the stomach, the spleen and splenic flexure of the colon, half the transverse colon and about 10 cm. of the descending colon. On looking through the opening in the diaphragm the lung was seen collapsed and the heart next to it in the same cavity had no pericardial covering. No symptoms or signs betrayed the absence of the pericardium. Another unusual anomaly not included in the classification given above, was reported by Barlow.<sup>3</sup> This was a case of displacement of the heart with fissure of the sternum and no covering of pericardium or skin. This baby lived 60 hours.

In Ingham and Willius's<sup>20</sup> report of 5 cases of transposition of the great arterial trunks, in 1 instance partial transposition was present, both the aorta and the pulmonary artery arising from the right ventricle. In the other 4 cases complete transposition was present. In 4 cases the ductus arteriosus was patent and in 4 instances the foramen ovale was patent. An interventricular septal defect occurred in 2 cases. In 2 cases situs inversus was associated with the interventricular septal defect. A systolic murmur was heard in 4 of the 5 cases. The age of death varied from 18 days to 7 months.

Goodson<sup>12</sup> reported 2 unusual cases of coarctation of the aorta. In 1 case death occurred at the age of 16 years as the result of the rupture of an aortic aneurysm into a small bronchus. The other case was a girl of 19 years, in whom the condition was discovered during the course of a routine physical examination of basketball players. These cases exemplified the chief diagnostic criteria of the condition; brachial hypertension with femoral hypotension, visible collateral circulation, systolic thrill with diastolic shock at the base, absence of the aortic knob and faint erosion of the ribs as revealed by Roentgen ray. In the case confirmed at autopsy there were observed as well a bicuspid aortic valve and an anomalous right coronary artery. The other case illustrated the fact that this condition is not incompatible with life and with apparently good health.

Semans and Taussig<sup>33</sup> recorded the presence of an enormous saccular dilatation of the left auricle in a 5-year-old child. The condition was believed to have been due to a congenital abnormality either in the blood supply of the affected area or in the auricular myocardium. The thickening of the mitral valve and shortening of the chordæ tendineæ are believed to have been associated with the congenital malformation of the heart. The fact that the enormous saccular dilatation of the left auricle extended to the left and that it occurred in conjunction with incomplete dextrocardia offered strong evidence that both conditions represented congenital anomalies.

Emenheiser<sup>10</sup> reported 10 cases of congenital dextrocardia. In this group there were 8 females and 2 males, all of whom were white persons. The usual mirror type of dextrocardia, with transposition of the abdom-

inal viscera, was found in 8 cases. Congenital dextrocardia with the thoracic aorta descending to the left side of the vertebral column without the transposition of abdominal viscera and unaccompanied by other serious anomalies was seen in 1 patient. Another showed the thoracic aorta descending on the right side of the vertebral column without the transposition of abdominal viscera, but accompanied by other serious anomalies. Electrocardiograms made in cases of congenital dextrocardia with transposition of the abdominal viscera showed the pathognomonic sign of inversion of all waves in Lead I and transposition of Leads II and III. The electrocardiograms made in the cases of congenital dextrocardia without transposition of abdominal viscera did not show these pathognomonic signs.

Taussig<sup>35</sup> gave the clinical and pathologic findings in congenital malformations of the heart due to defective development of the right ventricle and associated with tricuspid atresia or hypoplasia. The central feature in this congenital malformation is the diminutive size of the right ventricle. The associated malformations develop because the right ventricle does not function and as a result neither the tricuspid valve or the pulmonary valve can function so that both are either atretic or markedly hypoplastic. In addition, the only way for the blood to escape from the right auricle is through some defect in the interauricular septum. The extent of this defect determines whether the heart functions as a biloculate or triloculate organ. Clinically, the malformation is associated with persistent cyanosis and no murmurs. The diagnosis is established through the recognition of the very small size of the right ventricle. This gives a peculiar outline in the roentgenographic shadow. In the antero-posterior view, because of the absence of the pulmonary conus, the upper contour of the cardiac shadow immediately to the left of the sternum has a concave instead of a convex outline. In the left anterior oblique position the small size of the right ventricle is indicated by the absence of a cardiac shadow anterior to that of the aorta. These observations were substantiated by the electrocardiogram which shows a deviation of the axis to the left. The differentiation between functionally biloculate and triloculate hearts depends on the size of the interauricular septal defect. If there is a free communication between the two auricles or if the heart is functionally biloculate, physical examination yields no additional positive findings. When the interauricular septum is well formed it causes obstruction to the outflow of the blood from the right auricle. Under these circumstances the auricular pulsation is transmitted to the liver and is readily palpable at its margin. It is this pulsation at the edge of the liver, occurring in conjunction with the diminutive right ventricle, which distinguishes a functionally triloculate heart from one that is functionally biloculate.

Kugel<sup>22</sup> pointed out that only in recent years has it been demonstrated that in many cases so-called "idiopathic hypertrophy" of the heart was in reality associated with congenital malformations as well as rheumatic fever, glycogen-storage disease, myocardial degeneration of the heart and fibrosis. Cases of dilatation and hypertrophy of the heart associated with myocardial degeneration and fibrosis, constituted the majority of the cases. In most instances the causes and nature of

the enlargement of the heart in an infant could be determined. The chief features were enlargement of the heart without known cause, an afebrile course, the sudden onset of symptoms, dyspnea and cyanosis and the lack of signs or history suggestive of congenital heart disease, rheumatic fever, diphtheria, infections and anemia or metabolic disturbances. Some examples of this condition appear to be examples of von Gierke's glycogen-storage disease localized in the heart (Finkelstein<sup>11</sup>).

Radiologically, the diagnosis of congenital malpositions may be indicated by tracheal displacement in the inspiratory phase, according to Pendergrass and Allen.<sup>31</sup> They found this in 9 cases of congenital heart disease which at autopsy showed complete transposition of great vessels in 2 cases, partial transposition of great vessels in 2 cases, dextroposition of the aorta in 1 case, complete transposition of heart and great vessels in 1 case and multiple intrinsic defects in the heart in 2 cases. In 150 normal infants tracheal displacement did not occur in the inspiratory phase. They pointed out that in the normal at the thoracic inlet the trachea occupies practically a midline position in the postero-anterior view during the peak of the inspiratory phase of the respiration. From the thoracic inlet to the bifurcation of the trachea there is a slight deviation to the right. This is not true in the expiratory phase, at the height of which there is a marked buckling and deviation to the right. In the lateral view at the peak of the inspiratory phase the trachea occupies almost a straight course in its cervical and thoracic portions. In the expiratory phase there is some buckling of the trachea at the thoracic inlet associated with a moderate diminution in the caliber of the lumen.

Not only is congenital heart disease the result of malformations of the chambers and great vessels but there are reports of congenital heart disease due to other factors. Among these conditions is congenital heart block, according to Wallgren and Winblad,<sup>38</sup> first reported by Van der Heuvel in 1908. The most informative reports have been those of Yater and his collaborators in the United States, and Nielsen in Scandinavia. In order to make a definite diagnosis of congenital heart block it should be established by graphic records in a relatively young person without other apparent cause. Bradycardia must have been demonstrated at an early age. There must be no history of an infection that might have been responsible for the heart block. The total number of such cases in the literature is 77, which includes 2 cases reported by these authors. These showed fetal bradycardia. In 1 case the dissociation between the auricle and the ventricle was confirmed by fluoroscopic examination and in the other by electrocardiogram. In the first case at autopsy, although the heart was grossly normal, the bundle of His was interrupted for a short distance from the atrioventricular node by the fibrous tissue of the annulus fibrosus. In the other case, the ventricular septum was patent and the bundle of His was found only as a degenerated remnant, which lay in a strand of fibrous tissue and was separated both from the auricular muscle and from the normally developed portions of the ventricular conduction system. In the first patient the anomaly was regarded as of independent origin, but in the second it was evidently correlated with failure of formation of the interventricular septum.



Heubner<sup>18</sup> reported a case of congenital heart block. It was noted during delivery that the rate of the fetal heart sounds was extremely slow, not rising over 80 per minute even after the fetal head had entered the true pelvis. A healthy baby was born spontaneously. The heart rate was very slow, but no pathologic phenomena were noted on auscultation. The electrocardiogram showed bradycardia of 60 beats per minute. The auricular waves were not directly related to the ventricular complex and the *T* waves were diphasic in Leads II and III. In all probability there was a 2 to 1 block during and after birth. In other cases of congenital heart block reported in the literature the patients died a short time after birth and the autopsies showed severe defects. In this case there probably was a mild disorder which cleared up during the early months of the baby's development.

Harris<sup>16</sup> has reminded us that the treatment of a case of congenital heart disease is limited in its scope by the very nature of the condition. The lesions are present fully developed from birth. Treatment is confined, therefore, to adapting a damaged individual to a life which shall be as nearly normal as possible. In order to do this he recommended that it is necessary to determine to what degree the function of the heart has been damaged. In doing this the patients were classed into three groups. The first group consists of those who had such severe damage that they could not survive by more than a few days or weeks. The second group was made of those whose lesions, though severe, were compatible with a life of limited activity and stress. The third group were those who had congenital heart lesions, which did not interfere with cardiac efficiency. The second group was the one which deserved most consideration in the question of treatment. The management of these cases may be epitomized under three headings: the regulation of exercise, the anticipation and prevention of intercurrent disease, and education for a suitable vocation.

More active treatment was recommended in patent ductus arteriosus by Hubbard, Emerson and Green.<sup>19</sup> They emphasized the need of determining whether or not there was an arteriovenous shunt large enough to impair the normal cardiac function and the peripheral circulation. The evidence to be looked for was a delay in the growth and development of the child, any signs or symptoms of cardiac insufficiency and, more specifically, the signs of free aortic regurgitation, congestion or pulsation of the pulmonary vessels at the hilus of the lung as seen by Roentgen ray. These signs should be considered as danger signals and once they have been established surgical intervention should be considered in the hope of abolishing the excessive load on the heart, restoring normal circulation, allowing normal growth and eliminating the danger of heart failure. In reporting 4 cases in which patent ductus arteriosus was obliterated without mortality, Gross, Emerson and Green<sup>13</sup> stated that a persistently patent ductus arteriosus, after the first few years of life, was an important cardiovascular abnormality which may lead to serious and even fatal complications in adolescence or in adult life. The greatest of the impending dangers was subacute bacterial endocarditis. The next most important hazard was cardiac decompensation, which results from overwork of the heart produced by the arteriovenous communication. While most patients with patent

ductus arteriosus showed little or no disability during childhood, they are laying the foundations for later trouble by building atheromatous plaques in the pulmonary artery which may be later the site of bacterial vegetations, or they are so overexercising the heart that decompensation may occur one or two decades later. These authors claimed that, if operative ligation of the patent ductus arteriosus can be performed early in life, the degenerative changes in the pulmonary artery should be arrested and the danger of subsequent bacterial endocarditis should be decreased. At the same time ligation of the arteriovenous shunt greatly reduced the work of the heart and cardiac reserve should be increased.

In a number of studies on San Francisco school children Sampson, Christie and Geiger<sup>32</sup> found the percentage of children with congenital heart disease to be extremely high, and from this they concluded that the incidence of rheumatic heart disease was correspondingly low. In 13,338 school children 197 had heart disease. In this group the incidence of organic heart disease was 3.7 per 1000 of population, of which 2.2 had rheumatic heart disease and 1.4 congenital heart disease. This is interesting in passing but it is difficult to evaluate the relative hazard to the child of congenital heart disease and acquired heart disease unless more comprehensive statistics are available. This is not possible in a survey of school children but must include reports on babies who are stillborn, those that die in the neonatal period and even during the first years of childhood. This is necessary to get a proper conception of the rôle that congenital lesions play as usually only the less severe lesions allow survival up to the school age.

Turning to acquired heart disease among children, while rheumatic fever is its chief cause, the other infectious disease of childhood may result in similar residual damage to the heart. In a follow-up study of 1000 patients with rheumatic fever treated at the House of the Good Samaritan in Boston, Jones<sup>21</sup> found that at the end of 10 years 242 (24.2%) were dead, 310 were potential subjects of rheumatic heart disease and 427 had rheumatic heart disease. Of the 427 living patients with rheumatic heart disease there was no limitation of activity in 287, the limitation was moderate in 119 and in 21 there was a serious physical handicap. He stressed the importance of early recognition of the condition and the prevention of respiratory infections in these individuals.

Stroud, Goldsmith, Polk and Thorp,<sup>34</sup> in a study of 458 children, found that the average age of the primary manifestation of rheumatic fever was 7.3 years. Of the 307 children concerning whom information was available, 125 were dead or totally disabled and 182 were working or able to work or to go to school. Of a total of 428 primary manifestations and reactivations concerning which positive information was available, 61 % occurred during the months of December and May, with a peak of 15.2 % during March. Because of these figures they stressed the necessity of increased prophylactic care during these months in susceptible children between the ages of 6 and 10 years, as these are the years during which primary manifestations and reactivations are most apt to occur. In this group by far the greatest number of patients were Italian, Hebrew, American and Irish, in the order named. It was seen also that there was a familial incidence at least as high as

that in tuberculosis. As far as this study was concerned, measures to protect children with rheumatic heart disease from the common cold and other infections of the respiratory tract offered the most practical form of prophylactic treatment.

The natural history of rheumatic fever in the first three decades of life was the subject of a report by Wilson<sup>40</sup> of a 20-year period of observation on the course of the disease in 337 subjects. Of these, 225 had lived to ages of from 16 to 30 years and 112 had died of the disease. The onset from childhood was characterized by many varied manifestations of activity and by a varied number of years of freedom from recurrence or by continuous years of manifestation of active infection. After puberty, at about the age of 16 years, 66% of the subjects were free from recurrence of symptoms compared with the 13% before this age. The disease seemed to be self-limited, as death occurred in most instances of active carditis. The first attack of carditis was sometimes fatal, but the majority survived the first and even several subsequent attacks. The average at which death occurred was 12.6 years and the greatest incidence of death was in the group from 12 to 16 years. The type of rheumatic manifestation, exclusive of active carditis, did not appear to be of prognostic significance. The incidence of carditis was comparable whether the patient had pains in the joints alone, or chorea, or polyarthritides with or without pains in the joints. All of the subjects presented evidence of cardiac involvement, although in only 39% were the symptoms of carditis apparent clinically and in these patients the amount of cardiac damage was greater and the mortality higher. During the course of the disease physical signs of valvular involvement disappeared or were inconstant or uncharacteristic and led to considerable error as to the condition of the heart. The presence of considerable cardiac enlargement that could be demonstrated only by roentgenographic methods was an indication of the difficulty in establishing a diagnosis of cardiac hypertrophy by physical examination alone. Among those that survived, the majority were able to carry on their work without circulatory symptoms, and this was true especially of those past the age of puberty, and the author strongly emphasized the possibility that the idea that most rheumatic patients die in the third and fourth decades, was unfounded.

Cushing<sup>7</sup> indicated that heart disease was the most important cause of death now registered, as it accounted for 10% of all deaths and exceeded all other causes of death and disease, even including tuberculosis. In the careful routine examination of school children, from 2 to 5% show evidence of organic heart disease and of these 90% are due to rheumatic fever. Thus rheumatic heart disease is the outstanding threat against child health, and the seriousness of this is exaggerated by lack of knowledge. Stressing the needs in this direction, Jones<sup>20</sup> presented a plea for the early recognition of rheumatic fever which he considered the common cause of heart disease in children. Not only is it a threat against life but it often is the result of heart lesions that causes the individual to be a cardiac cripple. Marsh<sup>27</sup> also emphasized the same points and stated that the children with heart disease are just as truly crippled as those with bone deformities or paralyses.

Ball<sup>2</sup> pointed out that the major clinical manifestations of rheumatic disease are arthritis, carditis and chorea. He considered carditis as the most important as it most often leads to permanent damage. However, there is often some relationship of all three. Parrish, Taran and Starr<sup>30</sup> studied the incidence of cardiac disease in a group of children who had had one or more attacks of Sydenham chorea uncomplicated by any rheumatic manifestation and made a comparison of this incidence with the incidence of cardiac disease in a group of children presenting histories of chorea plus other manifestations of rheumatism. In this study 78 children had had one or more attacks of chorea without any rheumatic symptoms, while 34 had had both chorea and rheumatic symptoms. Of the entire group 59.8% had definite cardiac involvement. The incidence of cardiac involvement in the purely choreic group was 52.5% and in the mixed group 76.4%. While their figures do not agree with others previously published in one report, they do agree with the figures of another report and consequently the authors concluded that until the causes of rheumatism and chorea are better known, it would be advisable to assume that chorea is one of the rheumatic manifestations.

This opinion was held also by McCulloch.<sup>25</sup> In his paper he stated that it had been implied throughout his discussion that the chorea minor of Sydenham was a rheumatic manifestation and that such was the case was believed in his department. For this reason he suggested that the term encephalitis rheumatica was proper and more descriptive. It should serve to distinguish such cases from all others with a more obvious etiology or from those with idiopathic chorea of unknown etiology. Since the attack of chorea may be the first manifestation of the rheumatic state in the child, all cases must be watched for further fever. On the other hand, the rheumatic state may precede the chorea and there may be some overlapping in the diagnosis of all children. It was also suggested that the encephalitis of rheumatic fever was similar in its anatomic process to the arthritis, the acute pericarditis and myocardial changes of an exudative attack of rheumatic fever.

Diphtheria is regarded as an important factor in the development of acquired heart disease in childhood. Burkhardt, Eggleston and Smith<sup>6</sup> made serial electrocardiograms of 140 patients showing evidence of toxic diphtheria. Changes of contour were shown in 28 of these. In 23 cases the *T* wave changes occurred between the fifth and the thirteenth day of illness. The majority of changes occurred between the eighth and the fifteenth days of illness. In 17 cases conduction changes were shown between the fifth and thirteenth day of illness. In all of these cases atrioventricular dissociation developed and this complication invariably proved fatal. Fourteen patients died of toxic diphtheria. Diphtheria antitoxin in large doses was given to 7 of these on or before the fourth day of illness, so that it is evident that early administration of antitoxin did not give an advantageous result in this group of patients. Peripheral nerve palsies developed in 65% of the patients that showed electrocardiographic changes, but there was no apparent causal relationship to the cardiac phenomena. The essential histologic changes in the myocardium resulting from toxic

diphtheria are edema, congestion, cellular infiltration, degenerative changes in the muscle fibers and ultimately fibrosis. The electrocardiographic findings were recommended as an important guide to treatment. Where the serial electrocardiograms showed abnormalities it was necessary to maintain complete inactivity until there was a return to the normal.

As regards the myocardial changes, Oheim<sup>29</sup> studied 50 fatal cases of diphtheria in which there were no complicating infections or other complicating conditions. The successive changes were interstitial edema, myolysis, waxy degeneration, calcification, fatty degeneration, proliferation of fixed cells in the spaces arising from muscle cell degeneration, and leukocytic and lymphocytic infiltrations. Interstitial edema and initial myolysis appeared first on the second to the fourth day of the disease, while the other changes reached the height of intensity from the seventh to the thirteenth day. Repair by connective tissue proliferation had commenced by the tenth day. The most severe lesions were observed in the subendocardial and ring muscle layers of the myocardium, especially that of the right ventricle.

Scarlet fever as well as diphtheria comprised the study of Berger and Olloz.<sup>4</sup> They made electrocardiographic observations on 66 cases of scarlet fever and 31 cases of diphtheria. In 52 of these cases there were no clinical or electrocardiographic alterations, while in 14 cases there was evidence of cardiac affection. In their 31 cases of diphtheria 26 were normal both clinically and electrocardiographically.

Hartwell<sup>17</sup> stated that while cases of meningococcic septicemia are common in reports in the literature, those in which the accompanying endocarditis and myocarditis have been proved definitely were rare. He found only 17 case reports of endocarditis and 12 of myocarditis caused by the meningococcus. He reported a case that was proved at postmortem examination. In summing up all available material on the subject he stated that the patients usually died. The lesions were usually mitral in location and the myocardial lesions were probably more common than is recognized at the present time. Metastatic lesions were not infrequent, although there was difficulty in recognizing them clinically. Usually the diagnosis of the meningococcic septicemia was made by blood culture during the clinical course of the disease, but the endocarditis was frequently overlooked.

Thompson<sup>37</sup> reported the case of a 4-year-old girl who had whooping cough complicated by bronchopneumonia and an unusual degree of congestive heart failure, proceeding to general anasarca. There was no evidence of a preëxisting heart disease although there was a history of a faucial diphtheria some 8 months before. The author pointed out that some investigators maintain that apart from cardiac dilatation during the paroxysmal stage some attacks of pertussis have left permanent damage and even valvular disease. There are others who agree that a temporary mechanical strain may occur, affecting more particularly the right side of the heart, but heretofore there has been found no permanent damage either of the myocardium or of the endocardium.

While other infectious disease of childhood may cause cardiac lesions that are permanent, that carditis may occur with scurvy and other

nutritional disorders is not so generally known. Taylor<sup>36</sup> pointed out that Erdheim showed in 1918 that scurvy may be associated with cardiac lesions. Taylor's study was based on experiments with guinea pigs. It was found that guinea pigs suffering from scurvy showed cardiac valvulitis, myocarditis and occasionally pericarditis, often associated with Gram-positive organisms even when none had been injected. The lesions were commonest in the mitral valve, the auriculoventricular junction, the perivascular areas in the myocardium and the papillary muscles. Intradermal injections of hemolytic streptococci did not increase the incidence or severity of the lesions but increased the incidence with which the organisms were found in the heart. When infected guinea pigs were kept in a state of subacute scurvy for a considerable time, they acquired congestion of the lungs and liver. Once the lesions of the heart had developed, curing the scurvy did not remove the lesions, although it did prevent the development of congestive heart failure.

Along somewhat similar lines Waring<sup>39</sup> discussed nutritional heart disease although his observations were made on children instead of on experimental animals. It would seem that avitaminoses can be the cause of cardiac damage. In his cases he made the diagnosis of nutritional heart disease on the following findings: cardiac enlargement shown by percussion and by Roentgen examination and usually not accompanied by murmur; negative results of urinalyses; absence or sluggishness of reflexes; a history of a deficient diet, and more or less rapid response to rest and sufficient food. His 13 patients were children whose ages varied from 14 to 48 months and averaged 25 months. Only 1 was white. The cause of the cardiac enlargement did not appear in these cases. It was not known whether the deficiency of vitamin B<sub>1</sub>, deficiency of protein or general dietetic deficiency was the fundamental cause. These cases did not always manifest rapid reduction in size. Scurvy was not evident in these cases and rickets was not apparently active. All of the patients improved on adequate diets fortified with materials rich in vitamin B<sub>1</sub> such as brewer's yeast, wheat germ sugar and extract of rice polishings. In addition to these cases of cardiac disorder, 34 cases of nutritional edema without evident cardiac disease were observed. None of these had clinical cardiac enlargement nor Roentgen evidence of cardiac hypertrophy. In general, the histories and clinical conditions were similar to those of the children having cardiac lesions, and the age period incidences were parallel. It seemed probable that there were some cardiac changes that were not demonstrable. Electrocardiographic examination should be made as changes have been observed by this method in epidemic dropsy. These alterations included sinus tachycardia, sinus arrhythmia, short *P-R* interval, occasional auricular fibrillation, coronary *T* wave and other abnormalities of the *T* wave that suggested myocardial damage.

Hafkesbring, Drawe and Ashman<sup>44</sup> studied the electrocardiograms of 100 normal children in order to establish the normal variations. They found that the duration of the *P* wave averaged 0.062 second. The upper limit was 0.09 second. The height of the *P* wave in Lead I was slightly higher than the average for the adult and the upper limit should be placed at about 1.5 mm. A *P*<sub>2</sub> measuring over 2.5 should be con-

sidered above normal. A diphasic or slightly inverted  $P_3$  was occasionally found in the electrocardiogram of a normal child. Slight and questionable notching of the  $P$  wave was occasionally seen, but no definite or conspicuous notching of the  $P$  wave was found in the electrocardiogram of a normal child. The average  $P-R$  in this series was 0.132 second, and there was no significant difference according to sex. The  $P-R$  interval was found to show a tendency to increase with increasing age and to decrease with increasing heart rate. The average duration of the  $QRS$  phase was 0.065 second. The  $QRS$  showed an increase in duration with the increase in age.  $QRS$  of low voltage was found in only 1 of 100 electrocardiograms of normal children. There was no great difference in the heights of the  $R$  wave for children and those for the  $R$  wave of adults. The electrical axis in all but 3 cases ranged between 20 and 104 degrees and extended from a slight left axis deviation to a slight right axis deviation. Slight shifting of the  $RS-T$  segment, especially upward, was occasionally seen. The  $T$  waves consistently averaged higher for the boys than for the girls, even in different age groups.  $T_3$  was frequently inverted. Low  $T$  waves were found in only 1 case and this might not have been a perfectly normal individual. Premature beats were rare.

Studying children with rheumatic heart disease and congenital heart disease Drawe, Hafkesbring and Ashman<sup>8</sup> in the rheumatic group found that the principal abnormality of the  $P$  wave was definite and conspicuous notching, widening and slight increase in height. The  $P-R$  interval was definitely prolonged in a large percentage of cases of rheumatic heart disease. The abnormalities of the  $QRS$  complex were relatively slight, consisting of a small increase in duration and occasional notching or slurring of the individual waves. Only a slight tendency to right axis deviation was shown in the electrocardiograms of children with mitral stenosis and insufficiency. This was probably due to the fact that in most of these cases the condition was not far advanced. The children with aortic regurgitation showed a definite tendency to left axis deviation. The incidence of shifts of the  $RS-T$  segment was increased, but not so markedly as others have reported. Abnormalities of the  $T$  waves were found in 10% of the cases. These abnormalities consisted of low  $T$  waves in all leads, diphasic  $T$  waves in Lead I, and low, rounded, notched and inverted  $T$  waves in Lead II. The  $QT$  interval was often definitely prolonged. As with normal children the incidence of premature beats was low. Some children with rheumatic heart disease had normal electrocardiograms. In the children with congenital heart disease the outstanding abnormalities of the  $P$  wave were increases in the width and in the height, and these were found in the electrocardiograms of children with pulmonary stenosis and the tetralogy of Fallot and to a lesser degree in those of children with intraventricular septal defect. The notching of the  $P$  wave was not beyond normal limits. The  $P-R$  interval was approximately the same as it was in the electrocardiograms of the normal group. The average duration of the  $QRS$  was longer than in normal children. Notching and slurring of the  $QRS$  segment occurred frequently in children with pulmonary stenosis, occasionally in those with intraventric-

ular septal defect, and rarely in cases of patent ductus arteriosus. All the electrocardiograms of children with pulmonary stenosis showed extreme, conspicuous or definite right axis deviation. The  $T$  waves averaged considerably higher than the normal group, and the  $T$  waves of the males averaged considerably higher than those of the females. Abnormalities of the  $T$  wave were occasionally found, consisting of inversions of  $T_2$  and deep inversions of  $T_3$ . In a few instances the  $QT$  was slightly prolonged.

Another interesting contribution concerning electrocardiograms in children was the study of Lead IV in normal children and in ambulatory cases of cardiac disease by Messeloff and Pomerantz.<sup>23</sup> They found that the electrocardiograms of children were characterized by a marked variability in the form and the direction of its several components. Upright, diphasic and iso-electric  $T_4$  waves were normal findings in the tracings of children. In this series of tracings for ambulatory children with heart disease Lead IV supplied no information which was not secured from the three standard leads. For this reason it was concluded that there was no definite reason for the routine use of Lead IV for ambulatory children with heart disease.

As a concluding reference in this review it is in keeping with its importance to mention the observations of Hamburger.<sup>15</sup> He emphasized that cardiac capacity for work is more important than any condition that is disclosed by physical, Roentgen or electrocardiographic examination. With patients in bed without fever or involvement of joints the activity used in testing can be rising to the sitting position several times. For ambulatory patients it can be squatting or stair climbing. The physician can accompany and observe the child on a walk either over a level surface or uphill. Acceleration of respiration and dyspnea are more important points than the acceleration of heart action, which may be affected by psychic influences. Respirations should be observed without the child's knowledge.

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## PHYSIOLOGY

### PROCEEDINGS OF THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 21, 1940

**The Nature of the Permanent Diabetes Produced by Anterior Pituitary Extract.** F. C. DOHAN, C. A. FISH, and F. D. W. LUKENS (George S. Cox Medical Research Institute, University of Pennsylvania). Ten dogs have been made permanently diabetic by the injection of anterior pituitary extract (Young). The results of studies on these animals support the conclusions previously reached that, after it is established, the diabetes is comparable to pancreatic diabetes. The degree of the diabetes has varied but in 3 severely diabetic dogs the secretion of glucose and nitrogen during fasting is similar to that of totally depancreatized animals. The response to insulin, respiratory metabolism, and the consistent occurrence of marked atrophy of the islands confirm the early conception of the pancreatic nature of this condition. Our studies also show that after the termination of injections of pituitary extract the diabetes tends to become gradually more severe. This progress is retarded by insulin treatment, although no recovery of the atrophic islands has been noted.

**Respiratory Metabolism of the Porpoise.** LAURENCE IRVING, P. F. SCHOLANDER, and S. W. GRINNELL (Edward Martin Biological Laboratory, Swarthmore). As a species of small-toothed whale the porpoise, *Tursiops truncatus*, encounters the respiratory difficulties common to all whales. We have examined in 9 porpoises the characteristics of breathing and internal respiration in order to see how the respiration of whales proceeds and to gain light on how mammalian respiration operates when breathing is infrequent. During the course of our observations the porpoises usually breathed from 2 to 4 times a minute and during each respiratory pause the heart gradually slowed to about 40 beats per minute and then increased to about 80 a few seconds after taking a breath. Heart records were taken with the electrocardiograph.

During a 2-minute dive in the open sea the heart slowed to about 30 and remained retarded during active swimming under water. It appears likely that the bradycardia is associated with the elective control of circulation which is known to exist in several mammals during apnea. For comparison with the cardiac response in man it was found that the heart rate of a practiced and able diver at Silver Springs, Florida, slowed while he stood quietly under water to about 30. Even while swimming vigorously under water the bradycardia persisted. Measurements of the respiratory metabolism of porpoises weighing about 180 kg. by means of a large Krogh spirometer showed that each inspiration took in from 6 to 10 liters and about 10 % of that volume of oxygen was utilized. The resting oxygen consumption was about 1 liter per minute. At each expiration the lungs were almost completely emptied, the residual air being determined at about 20 % of the inspired air. The alveolar  $\text{CO}_2$  was between 7 and 10 %. It appears that porpoises are like several other diving animals which are relatively insensitive to  $\text{CO}_2$ . During or after a forced dive of 2 or 3 minutes' duration it was remarkable that the alkali reserve of the blood changed very little, and scarcely any increment of lactic acid appeared either in blood or muscles. Although fatal asphyxia could be caused in 3 minutes the absence of the acid as a sign of anaerobiosis was surprising. These observations point out the mechanics and dimensions of the respiratory system in the porpoise. They also show how certain typical mammalian respiratory mechanisms operate under the peculiar conditions in which an aquatic mammal lives.

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**How Do We Perceive the Pulse?** F. H. LEWY and B. Lewy (by invitation) (Department of Neurosurgery, University of Pennsylvania). The arterial pulse can be felt by palpation by only a few areas of the body surface, namely the volar surfaces of the fingers and hand, the plantar surfaces of the toes and the heel, the lips, and the tongue when passively pressed against the artery. The acuity of perception of pulsation follows Weber's scala for spatial discrimination. The skin areas sensitive to pulsation are invested with the greatest number of touch points per square centimeter, and their sensory nerves have the greatest velocity of conduction. Thus, the skin areas sensitive to the pulse beat possess the two main prerequisites of stereognosis. "Feeling the pulse" is a stereognostic function because, in addition to counting the frequency of the pulse beats, the examiner is concerned with appreciation of the profile of the pulse wave, the recognition of its qualities, and with its classification.

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**Excretion of Sodium Pregnandiol Glucuronidate in Urine of Normal Human Pregnancy.** C. BACHMAN, D. LEEKLEY, and H. HIRSCHMANN (Gynecean Institute, University of Pennsylvania). The method of Venning and Browne for the recovery of pregnandiol glucuronidate from urine was employed for a study of the excretion of this compound during normal gestation in 6 healthy young women. The results fully confirmed the

earlier findings of Venning, Henry and Browne concerning the quantities excreted at various periods of normal pregnancy. In addition, excretion during gestation in our cases was marked by slight cyclic monthly remissions, and by a pre-labor fall. Additional data, obtained from 4 cases of multiple gestation, suggested that the quantities of pregnandiol glucuronide excreted in such cases did not differ significantly from those excreted at corresponding periods of single-fetus gestations.

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ORIGINAL ARTICLES.

PERNICIOUS ANEMIA.

THE ERYTHROCYTE RESPONSE TO TREATMENT.

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SOON after their discovery of the therapeutic effectiveness of liver in pernicious anemia, Minot and his associates<sup>3,4</sup> recognized certain quantitative relationships between the erythrocyte count before treatment, the dose of liver employed in treatment, the number of reticulocytes which appeared early in remission, and the increase in the erythrocyte count. They were impressed particularly by the importance of the large number of reticulocytes in the blood in the first phase of the remission following liver therapy. They and others<sup>1,3,4,6</sup> devised mathematical equations which represent the numbers or percentage of reticulocytes which may be expected to appear in individual patients with pernicious anemia who are adequately treated. Although these standard reticulocyte equations have proven useful in the estimation of the clinical effectiveness of the various therapeutic agents, in the regulation of their dosage, in the clinical management of patients and in the assaying of materials of unknown therapeutic potency, their value for these purposes has been disputed, particularly by Murphy.<sup>5a,b</sup> He questions the accuracy of the reticulocyte response as a quantitative index of the amount or potency of therapeutic agents used in pernicious anemia. He believes the increased numbers of reticulocytes after treatment serve qualitatively to indicate the presence of active material in the substance used in treatment but cannot be used as a quantitative measure of the amount of the active material administered. This opinion is based upon the apparent lack of correlation in his cases between the amount of active liver

principle given and the magnitude of the reticulocyte response on one hand, and the magnitude of the erythrocyte increase on the other. He maintains that the increase in the numbers of erythrocytes during treatment is more accurate an index of the potency and amount of the active liver principle administered. Using the average increase in the erythrocyte count per day as an index of the effectiveness of treatment he finds, in his cases which received liver extract derived from 100 to 300 gm. of liver given intramuscularly during the first week of treatment, that the average daily increase in the erythrocyte count during the first 2 weeks of treatment varies from 128,000 to 54,000 per c.mm. of blood in patients whose initial erythrocyte counts ranged from 1 to 3.5 millions per c.mm. The highest values were found when the erythrocyte count was low.

Obviously, the rise in the erythrocyte count in response to therapy would be a far simpler method of evaluating the effect of treatment than the reticulocyte response if the expected erythrocyte increase were expressed in as simple and accurate form as the standard reticulocyte equations. With this in mind a large number of remissions have been studied to determine the quantitative relationships between the rate of erythrocyte increase and the erythrocyte count before treatment.

**Materials.** The present study is devoted to an analysis of the quantitative relationships existing in 600 patients with pernicious anemia, between the erythrocyte count before treatment and the increase in the numbers of erythrocytes after treatment. These patients had the typical clinical manifestations of pernicious anemia and the characteristic blood findings associated with this disease. A certain number, as would be expected in so large a group, had the various complications commonly associated with pernicious anemia, in varying degrees of severity. Rarely the presence of cancer of the stomach, surgical removal of large parts of the stomach, lesions of the liver and other conditions provided a possible anatomic cause for the hematologic and clinical picture of pernicious anemia. These patients had in common a macrocytic anemia which responded with the familiar reticulocyte response and an increase in the number of circulating erythrocytes when adequate amounts of therapeutic materials were given. To study the problem in all its manifestations every remission was recorded, whether satisfactory or not. All cases showing an increase in the number of reticulocytes above 3% were recorded. Among the 600 cases studied, 597 remissions were tabulated in which sufficient data were present to be of value. Various types of treatment were used. For convenience in analysis, therapy was listed under five classifications: 1, Intravenous liver extract; 2, intramuscular liver extract; 3, ventriculin; 4, oral liver extract; 5, miscellaneous.

In the last of these classifications the patients were treated with experimental extracts of liver, stomach and other organs given orally, rectally and parenterally; yeast products; gastric juice; and gastric juice and meat. Spontaneous remissions were also included in this group.

The data, red blood cell counts, reticulocyte estimations, cell measurements, and so on, were most abundant. These estimations were carefully performed by accepted methods, with standardized instruments, by competent technicians.

*The Relationship Between the Increase in the Erythrocyte Count and the Initial Level of the Erythrocyte Count.* Classifying the 597 remissions according to the type of treatment used, five groups were obtained. There were 114 patients who received liver extract orally, 149 who were given ventriculin, 85 who received liver extract intramuscularly and 175 to whom liver extract was administered intravenously. The remaining 74 patients had spontaneous remissions or were treated experimentally with various substances. This last group furnished variable data unsatisfactory for analysis. The remaining four groups were sufficiently large and homogenous to determine with considerable accuracy the relationships existing between the increase in the erythrocyte count and the initial erythrocyte count taken before treatment. To determine this relationship each of these groups was subdivided according to the erythrocyte count before treatment at 0.5 million intervals. Next each of these subdivisions was divided arbitrarily into three equal groups according to the percentage of reticulocytes present at the peak of the response. The patients in the subdivisions with the lowest reticulocyte percentages were arbitrarily considered to be "unsatisfactorily treated." The average weekly increase in the erythrocyte count for the remaining 349 patients "satisfactorily treated" was computed after the first 2 weeks of treatment. When the average weekly increase in the erythrocyte count in this group was plotted graphically (Fig. 1) the equation  $I = 0.78 - 0.174E_o^*$  was obtained. In the same manner, the average weekly increase in the erythrocyte count for the "unsatisfactorily treated" group of 174 patients, the equation  $I = 0.6 - 0.176E_o$  was obtained.

The results of this procedure when applied to the various treatment groups of "satisfactorily treated" cases, receiving oral liver extract, ventriculin, intramuscular and intravenous liver extract are shown in Table 1.

TABLE 1.—EQUATIONS REPRESENTING THE OBSERVED AVERAGE WEEKLY INCREASE IN THE ERYTHROCYTE COUNT IN VARIOUS GROUPS OF PATIENTS UNDER DIFFERENT TYPES OF TREATMENT AFTER 2 WEEKS OF TREATMENT.

Method of treatment.		
1. Oral liver extract, "satisfactorily treated" . . . . .	I =	$0.78 - 0.177E_o$
2. Ventriculin, "satisfactorily treated" . . . . .	I =	$0.70 - 0.171E_o$
3. Intramuscular liver extract, "satisfactorily treated" . . . . .	I =	$0.78 - 0.175E_o$
4. Intravenous liver extract, "satisfactorily treated" . . . . .	I =	$0.88 - 0.175E_o$
5. Average of all "satisfactorily treated cases" . . . . .	I =	$0.78 - 0.174E_o$
6. Average of all "unsatisfactorily treated cases" . . . . .	I =	$0.60 - 0.176E_o$

In these various equations, the positive values vary widely from 0.6 in the case of "unsatisfactorily treated" patients to 0.88 in the group of patients treated satisfactorily with intravenous liver extract. The numerical value of this positive factor appears to be

\* I represents the average weekly increase in the erythrocyte count during the first 2 weeks of treatment,  $E_o$  the erythrocyte count before treatment in millions per c.mm. of blood.

directly proportional to the effectiveness of treatment. On the other hand, the negative values in the various equations are all approximately the same, the range of variation being from  $0.171E_0$  to  $0.177E_0$  and the average value being  $0.174E_0$ . These negative values being uniform regardless of the type or effectiveness of treatment must have no relationship to the effectiveness of treatment and, being proportional to the erythrocyte count before

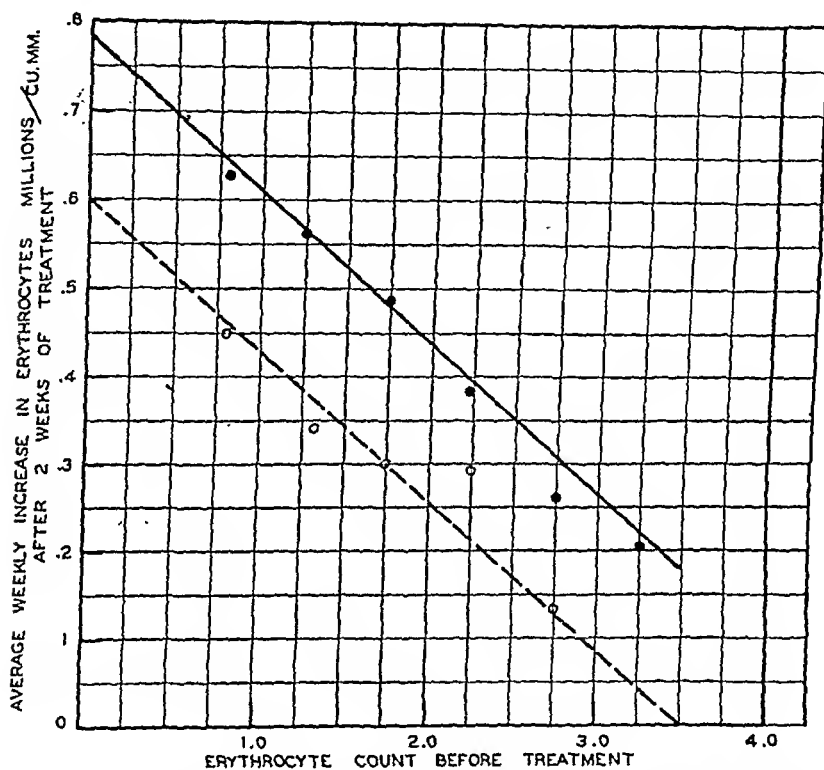


FIG. 1.—The relationship of the weekly increase in the erythrocyte count to the erythrocyte count before treatment in "satisfactorily" and "unsatisfactorily" treated patients with pernicious anemia after the first 2 weeks of treatment. *Solid dots*: average observed values of the weekly increase in the erythrocyte count with "satisfactory" treatment. *Solid line*: the average weekly increase in the erythrocyte count in "satisfactorily" treated patients, calculated from the equation  $I = 0.78 - 0.174E_0$ . *Open circles*: average observed values of the weekly increase in the erythrocyte count with "unsatisfactory" treatment. *Broken line*: the average weekly increase in the erythrocyte count in "unsatisfactorily" treated patients calculated from the equation  $I = 0.60 - 0.176E_0$ .

treatment, they must bear a direct relationship to the character or numbers of the erythrocytes present during relapse.

These equations, which are derived from data taken at the end of the first 2 weeks of treatment were found to be valid in all cases only for this period. The rise in the erythrocyte count is not uniform throughout the remission, being rapid at first and slower toward the end of the remission. In patients with low initial erythro-

cyte values this difference in the rate of erythrocyte increase in successive weeks is more noticeable than those with higher erythrocyte counts.

The equation  $I = 0.78 - 0.174E_o^*$  is offered as a standard for the relative effectiveness of treatment of any type in patients with pernicious anemia. The expected average normal values as determined from this equation are tabulated in Table 2. This equation represents an erythrocyte response which will result eventually in an erythrocyte count of about 4.5 million per c.mm. of blood in from 6 to 8 weeks of treatment depending upon the level of the erythrocyte count before treatment.

Patients with an average weekly increase in the number of erythrocytes at the end of 2 weeks of treatment which is less than that expected from this equation will eventually have an erythrocyte count less than 4.5 million per c.mm. of blood, if the erythrocyte response continues at the same magnitude. Empirically, it has been determined from the data available that if the positive value in the equation is about 0.9 the eventual erythrocyte count will be approximately 5 million per c.mm., if it is 0.7 about 4.15 million per c.mm. of blood, if the dosage of the therapeutic material is not varied during the period involved. The end of the first 2 weeks of treatment is chosen as the most desirable time to estimate the average weekly increase in test patients. This test period of 2 weeks duplicates the conditions under which the standard values are derived. Beyond this 2-week period comparable values will not be obtained if the original erythrocyte count is low. Technical errors in the estimation of the erythrocyte counts before treatment and after treatment from which the increase in the erythrocyte count is estimated are minimized by choosing a period longer than 1 week.

If it is desired to compare the effect of a sample of some particular therapeutic material to the average effect of the doses of material of known potency which are customarily used, the equations which deal with the material in question can be used as standards. For example, a sample of intravenous liver extract of unknown potency is given in the usual dose of 20 cc. per week (prepared from 100 gm. of liver) to a patient with pernicious anemia whose initial erythrocyte count is 1 million per c.mm. of blood. The average weekly increase in the erythrocyte count is calculated at the end of the second week of treatment from observed erythrocyte counts and found to be 0.710 million per c.mm. of blood. The expected value from the equation  $I = 0.88 - 0.175E_o$  (Table 1, Equation 4) under these circumstances is 0.705. Thus the erythrocyte response is that which would be expected from the same dose of liver extract of average potency. If, however, the observed value was 0.500,

\* Average weekly increase in erythrocyte count millions per c.mm., (I) equals 0.78 minus 0.174 times the initial erythrocyte count millions per c.mm. ( $E_o$ ).



the tested extract obviously would be inferior in potency as compared to the standard intravenous liver extract.

*Untoward Factors Which Affect the Interpretation of the Erythrocyte Response.* In the interpretation of the reticulocyte response by means of the standard reticulocyte equations<sup>1,3,4,5</sup> in common use, many factors which may alter the magnitude of the reticulocyte response must be considered if the correct conclusions are to be reached. Most of these same factors also affect the erythrocyte response. Any alteration of the concentration of the erythrocytes in the blood as might result from hemorrhage, transfusion, or hemolysis unnatural to pernicious anemia alter the values of the erythrocyte increase. Any change in the fluid content of the blood, as by dehydration, likewise produces unsatisfactory results. Other disorders, present as complications of pernicious anemia, which affect erythropoiesis affect the erythrocyte response. Recent treatment makes the interpretation of the erythrocyte response unreliable. Unsuspected spontaneous remissions likewise may affect the reliability of interpretation of the results in some cases. Technical, mechanical and human errors in the estimation of the erythrocyte count are a constant source of error. The mathematical error inherent in measurements of any sort is a constant source of error in erythrocyte counts. Under the most scrupulous technique errors of this type of 200,000 cells per c.mm. are not unusual. Since erythrocyte counts are the basis of these equations the normal probability of such an error must be considered in the interpretation of results in individual cases. This error is lessened if the average of several estimations of the erythrocyte count for the value is used in the necessary computations.

*The Relation of the Dose of Therapeutic Material to the Erythrocyte Response.* On studying the erythrocyte response in this large number of patients with pernicious anemia, the magnitude of the erythrocyte response as measured by the average weekly increase in the concentration of the erythrocytes in the blood during the first 2 weeks of treatment is found to be directly in proportion to the effectiveness of treatment and the size of the effective dose of the material used. The determination of the exact nature of the latter relationship is impossible from the data at hand. The exact relationship between the therapeutic dose and the erythrocyte response can be found only under the rigid experimental conditions pointed out by Minot<sup>2</sup> in a consideration of the same problem in relation to the reticulocyte response.

Important among the conditions necessary in such an experiment are exclusion from the diet of sources of the extrinsic factor or of other sources of the pernicious anemia principle than the therapeutic material used; use of doses of the therapeutic material sufficiently small to produce an average or less than average erythrocyte response; elimination of test patients in whom factors are present

which alter the concentration of erythrocytes in the blood or alter erythropoiesis and the use of a single lot of therapeutic material of uniform potency in varying doses in patients with a similar degree of anemia.

*Comparative Usefulness of the Reticulocyte Response and the Erythrocyte Response in Evaluating the Effectiveness of Treatment.* The standard reticulocyte equations have been very useful in the standardization of liver extracts and in adjusting the therapeutic dosage to the needs of individual patients, although there has been some doubt expressed as to their value for these purposes.<sup>5a,b</sup> The use of the reticulocyte response in the evaluation of the effect of treatment in pernicious anemia has certain obvious practical disadvantages as compared with the use of the erythrocyte response. The erythrocyte response has similar disadvantages in this regard. With certain reservations, far more is known of the laws which govern the behavior of the reticulocytes in relation to treatment than is known regarding the rise in the erythrocyte count. Practically speaking, the most exact correlated data available for use in the literature for comparing the changes in the erythrocyte count in relation to the dosage of therapeutic material are found in the articles by Murphy.<sup>5a,b</sup> These particular data represent the increase in the erythrocyte count in a highly specialized form of treatment in which relatively large doses of liver extract are administered at infrequent intervals. They represent approximately the maximum erythrocyte response possible to obtain with large doses of liver extract. A rise in the erythrocyte count of similar magnitude was observed in a large proportion of the patients receiving intravenous liver extract in the present study. The eventual clinical improvement in these patients was no more satisfactory and the eventual level of the erythrocyte count was no greater than in many other patients who were given comparatively smaller doses of liver extract or ventriculin more uniformly during the period of remission.

Essentially the same situation exists in the interpretation of the reticulocyte response. As compared to values in the original standard reticulocyte curve designed for use in patients treated orally with liver extract<sup>6</sup> the average maximum reticulocyte percentages observed in patients treated with intravenous liver extract<sup>1</sup> are much greater. Nevertheless, the clinical improvement and the eventual level of the erythrocyte count were equally satisfactory under both types of treatment in adequately treated cases. The point of the matter is that a standard to be satisfactory should represent the minimum erythrocyte response which will result in the desired clinical and hematologic improvement.

The various standard reticulocyte equations<sup>1,3,4,6</sup> have counterparts in the various standard equations for the erythrocyte response set forth here. The equation  $I = 0.78 - 0.174E_0$  which serves in general as a standard for the average erythrocyte increase under all

types of treatment and in particular for the erythrocyte increase with the customary treatment with liver extract orally (daily dosage of liver extract derived from 300 to 500 gm. of liver during early remission) and for the treatment with liver extract intramuscularly (in daily dosage of liver extract derived from 10 to 15 gm. of liver) has an almost identical significance with the standard equations for the reticulocyte response used in patients treated with oral liver extract ( $EpR = 0.73 - 0.2Eo^3$  and  $R = \frac{0.73 - 0.2Eo^3}{0.73 + 0.8Eo}$ ).

TABLE 2.—THE AVERAGE WEEKLY INCREASE (I) IN THE ERYTHROCYTE COUNT TO BE EXPECTED IN PATIENTS WITH PERNICIOUS ANEMIA AFTER 2 WEEKS OF ADEQUATE THERAPY AT VARIOUS LEVELS OF THE ERYTHROCYTE COUNT BEFORE TREATMENT ( $Eo$ ).

Calculated from $I = 0.78 - 0.174Eo$ .					
$Eo$ .	Millions per c.mm.	I.	$Eo$ .	Millions per c.mm.	I.
0.5 . . . . .		0.693	2.5 . . . . .		0.345
0.6 . . . . .		0.676	2.6 . . . . .		0.328
0.7 . . . . .		0.658	2.7 . . . . .		0.310
0.8 . . . . .		0.641	2.8 . . . . .		0.293
0.9 . . . . .		0.623	2.9 . . . . .		0.275
1.0 . . . . .		0.606	3.0 . . . . .		0.258
1.1 . . . . .		0.589	3.1 . . . . .		0.241
1.2 . . . . .		0.571	3.2 . . . . .		0.223
1.3 . . . . .		0.554	3.3 . . . . .		0.206
1.4 . . . . .		0.536	3.4 . . . . .		0.188
1.5 . . . . .		0.519	3.5 . . . . .		0.171
1.6 . . . . .		0.502	3.6 . . . . .		0.154
1.7 . . . . .		0.484	3.7 . . . . .		0.136
1.8 . . . . .		0.467	3.8 . . . . .		0.119
1.9 . . . . .		0.449	3.9 . . . . .		0.101
2.0 . . . . .		0.432	4.0 . . . . .		0.084
2.1 . . . . .		0.415	4.1 . . . . .		0.067
2.2 . . . . .		0.397	4.2 . . . . .		0.049
2.3 . . . . .		0.380	4.3 . . . . .		0.032
2.4 . . . . .		0.362	4.4 . . . . .		0.014

The equation  $I = 0.78 - 0.174Eo$  and  $EpR = 0.73 - 0.2Eo^3$  have obvious similarities and were derived in a similar manner, by a comparison of averages of the observed data to the erythrocyte count before treatment.

In Table 3 the comparison is made between the relative dosage of ventriculin and liver extract administered in various ways; the observed average weekly increase in the erythrocyte count after the first 2 weeks of treatment and the values for the expected weekly increase in the erythrocyte count as calculated from the equation  $I = 0.78 - 0.174Eo$ . The observed and expected values of the increase in the erythrocyte count were approximately the same in the patients in this series treated with oral and intramuscular liver extract at all levels of the erythrocyte count before treatment. The observed values with ventriculin were usually considerably lower than the expected values. The observed values from the patients given intravenous liver extract in this series and

from the patients whose data are reported by Murphy<sup>5a,b</sup> are considerably higher than the expected average normal values calculated from the equation  $I = 0.78 - 0.174E_0$ . These differences in the observed and calculated values are obviously related to the weekly effective dose administered in each group. The high values observed in the patients receiving liver extract intravenously and in Murphy's patients do not necessarily indicate that the eventual erythrocyte count will be proportionately greater or that

TABLE 3.—COMPARISON OF THE INCREASE IN THE ERYTHROCYTE COUNTS IN PERNICIOUS ANEMIA AFTER THE FIRST 2 WEEKS OF TREATMENT UNDER VARIOUS TYPES OF THERAPY.

Type of treatment.	Number of cases.	Average weekly dose, gm.	Range of R.B.C. before treatment.	Average R.B.C. before treatment.	(I) Average weekly increase R.B.C., millions per c.mm. (observed).	Normal average weekly increase R.B.C., millions per c.mm. (calculated $I = 0.78 - 0.174E_0$ ).
Oral liver extract	12	3800*	0.5-1.0	0.79	0.693	0.643
	22	3800	1.0-1.5	1.28	0.560	0.557
	14	3350	1.5-2.0	1.77	0.434	0.472
	14	3400	2.0-2.5	2.21	0.427	0.396
	6	3500	2.5-3.0	2.70	0.280	0.310
	6	3400	3.0-3.5	3.39	0.182	0.191
Ventriculin	12	270	0.5-1.0	0.78	0.384	0.644
	23	255	1.0-1.5	1.25	0.490	0.562
	23	278	1.5-2.0	1.72	0.462	0.481
	22	244	2.0-2.5	2.17	0.364	0.402
	13	250	2.5-3.0	2.73	0.224	0.305
Intramuscular liver extract	4	85*	0.5-1.0	0.90	0.637	0.623
	12	98	1.0-1.5	1.26	0.581	0.561
	15	98	1.5-2.0	1.78	0.462	0.471
	13	80	2.0-2.5	2.19	0.315	0.399
	9	55	2.5-3.0	2.74	0.182	0.303
Intravenous liver extract	16	100*	0.5-1.0	0.82	0.721	0.635
	22	to	1.0-1.5	1.25	0.671	0.562
	27	98	1.5-2.0	1.69	0.581	0.490
	19	95	2.0-2.5	2.22	0.560	0.394
	19	105	2.5-3.0	2.67	0.357	0.315
	8	95	3.0-3.5	3.15	0.182	0.232
Intramuscular liver extract (Murphy <sup>5a,b</sup> )	..	200*	1.0-1.5	1.23	0.895	0.570
	..	to	1.5-2.0	1.75	0.685	0.475
	..	300	2.0-2.5	2.26	0.625	0.387
	..	..	2.5-3.0	2.74	0.525	0.303
	..	..	3.0-3.5	3.34	0.490	0.299

\* Liver extract in terms of grams of liver from which extract is derived.

the normal erythrocyte count will be achieved sooner than in the patients in the groups treated with oral and intramuscular liver extract. The average erythrocyte counts observed in these variously treated patients were practically the same (about 4.6 millions per c.mm.) at the end of the sixth week of treatment both in the patients reported by Murphy and those reported here. On the other hand, in the patients treated with ventriculin in whom the erythrocyte response at the end of 2 weeks of treatment was under

the expected normal value, the average erythrocyte count was about 3.9 million per c.mm. at the end of the sixth week of treatment.

Observed values of the average weekly increase in the erythrocyte count at the end of the second week of treatment equal to or higher than the values calculated from the equation  $I = 0.78 - 0.174E_0$  indicate the return of the erythrocyte count to a normal level 4.5 to 5.5 million per c.mm., within 2 months of treatment, if adequate treatment is continued throughout the period. Observed values for the average weekly increase in erythrocytes at the end of 2 weeks of treatment distinctly under the calculated values signify inadequate treatment. In such cases, the eventual erythrocyte count will be distinctly less than normal unless the amount of treatment is increased.

When the standard reticulocyte equations<sup>1,3,4,6</sup> and the proposed standard equations of erythrocyte increase are used in the manner suggested here, in individual patients satisfactory for the purpose similar conclusions as to the adequacy or inadequacy of treatment will be arrived at by either method. Neither the reticulocyte response nor the erythrocyte response is superior for the purpose of estimating the effectiveness of treatment. The two methods should be used in conjunction with one another, one verifying the significance of the other.

**Summary.** 1. From data in 523 patients with pernicious anemia satisfactorily treated, the average weekly increase in the erythrocyte count at the end of 2 weeks of treatment was found to bear an inverse relationship to the erythrocyte count before treatment.

2. This relationship is expressed in the equation  $I = 0.78 - 0.174E_0$  where  $I$  is the average weekly increase in the erythrocyte count after 2 weeks of treatment and  $E_0$  the erythrocyte count before treatment expressed as millions of erythrocytes per c.mm. of blood.

3. This equation is suggested as a standard for measuring the relative effectiveness of treatment in pernicious anemia.

4. Observed values equal to or greater than those obtained from this equation indicate adequate treatment. Observed values less than those calculated from the equation indicate inadequate treatment.

5. The existence of various complicating factors such as concurrent disease, transfusion or hemorrhage in association with pernicious anemia, invalidate the use of this standard.

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## THE BLOOD OF NEWBORN RATS AFTER ORAL ADMINISTRATION TO THE MOTHER OF NORMAL AND ABNORMAL HUMAN GASTRIC JUICE.\*

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ONE of the more conspicuous gaps in our knowledge of pernicious anemia is the lack of any reliable, non-clinical, laboratory test for the detection of antianemic factor and for the determination of the potency of therapeutic antianemic preparations. In spite of considerable work on the subject there is still no accredited test or assay technique which does not require the use of relapsed pernicious anemia patients. Since there is no condition in animals comparable to true pernicious anemia in man, investigation has been limited to the effects of the administration of antianemic substances to normal animals or to animals with artificially induced anemia, and to certain biochemical tests.

Studies on normal animals have been concerned chiefly with attempts to alter the number of circulating reticulocytes. Investigations of this type led to the "pigeon test" of Vaughan, Muller and Zetzel,<sup>17</sup> the "guinea-pig test" of Jacobson<sup>10</sup> and the "rat reticulocyte reaction" or "R. R. R. test" of Singer.<sup>14</sup> The blood of dogs, rabbits, pigs and sheep also has been investigated from this standpoint.

Experimental anemia has been induced in animals by the injection of various toxins and bacteria, by feeding deficient diets and by extensive bleeding. The reports which have appeared regarding any specific value of antianemic substance either in preventing or in remedying induced anemia are most conflicting. The earliest biochemical tests concerned the supposed property of antianemic extracts of forming methemoglobin when added to a suspension of washed erythrocytes.<sup>7</sup> More recently the enzymic properties of the "intrinsic factor" as a proteolytic agent have been investigated.<sup>8,12,16</sup> In general, laboratory methods have not yielded uniform or satisfactory results. Each test has its advocates, but widespread confirmation of any one has not been forthcoming.

A recent approach to the problem was an attempt to influence the rate of maturation of the blood in the developing fetus. The resemblance between the cells of fetal blood and those of the blood of patients with pernicious anemia has long been recognized, but Wintrobe and Shumacker<sup>22</sup> were the first to point out the similarity between the changes which occur in fetal blood as development proceeds and the changes occurring in the blood of an adequately treated patient with pernicious anemia. They suggested that the

\* This work was done in the Division of Experimental Medicine, The Mayo Foundation.

same stimulating influence might be responsible for the changes which take place in both conditions. If this were the case, it should be possible to hasten the maturation of fetal blood by making available to the fetus an excess of antianemic factor, on the assumption that delayed maturation was due to a relative deficit of the maturation factor. It has been demonstrated of course that fetal tissues are not wholly devoid of the antianemic principle.<sup>19</sup>

The first attempt to influence fetal hemopoiesis was made by Wintrobe and his coworkers in 1937.<sup>21</sup> They were unable to alter the blood picture of fetal rabbits by the intramuscular injection of liver extract into the mother during pregnancy or by injection directly into the placenta at laparotomy. Stasney, Higgins and Mann<sup>15</sup> reported an increase in the number of circulating erythrocytes and a decrease in erythrocyte volume and diameter in the blood of newborn rats whose mothers had received daily intraperitoneal injections of concentrated gastric juice from normal human beings or from the fundic pouch in a hog. The effect of the gastric juice was proportional to the number of injections the mother had received. Heating the gastric juice prior to injection completely eliminated the effect on fetal blood. This led Stasney and his coworkers to conclude that normal human and swine gastric juice contained a substance capable of accelerating erythrocyte maturation in fetal rats.

Briese and Higgins<sup>2</sup> reported reductions in the diameters of erythrocytes of newborn rats whose mothers were fed ventriculin during pregnancy. These findings have been held to confirm the hypothesis that the physiologic macrocytosis of the mammalian fetus is due to a lack of adequate amounts of the antianemic principle. By still further reducing the amount of antianemic principle available to the fetus by damaging the liver of the mother by carbon tetrachloride inhalation, Briese<sup>1</sup> concluded that she was able to exaggerate the macrocytic anemia of newborn rats. Jones<sup>11</sup> studied blood smears prepared from the yolk sac of the 11-day rat embryo following parenteral injection of liver extract into the mother during pregnancy and observed a decrease of mean cell diameter and still greater decrease of mean nuclear diameter. These changes, along with the increased polychromatophilia, pyknosis and karyorrhexis which he noted, Jones interpreted as indicating an acceleration of cytoplasmic differentiation and nuclear maturation produced by the transmission of a superabundance of antianemic principle across the placenta.

Wigodsky and Ivy<sup>18</sup> were unable to detect any change in the blood of newborn rats to whose mothers they administered liver extract intraperitoneally during pregnancy. Bruner<sup>3</sup> reported similar negative results after the intramuscular injection of liver extract into pregnant rats. Reimer<sup>13</sup> was unable to detect any changes in the blood, liver or bone marrow of chick embryos after injecting

liver extract into the whites of intact eggs. Injections into the allantois were also performed, but no difference was noted between the treated embryos and untreated controls.

The study of the factors concerned with fetal hemopoiesis only recently has arrived at the experimental stage. A great deal of work will have to be done before any conclusions can be drawn regarding the possible identity of factors operative in the embryo and curative in pernicious anemia. Aside from the academic value of such studies, it is apparent that, if it can be demonstrated that fetal hemopoiesis can be accelerated by antianemic preparations, then a whole new field lies open for the further investigation of methods for detecting the presence of antianemic factors and testing the potency of materials containing them.

**Methods.** Samples of human gastric juice, collected after ingestion of a test meal of arrowroot biscuits and water, were obtained from the gastroenterologic laboratory. These were filtered, pooled in several different lots and refrigerated until needed. The first lot was composed of specimens considered to represent normal gastric secretion, containing 20° to 40° of free hydrochloric acid (Töpfer's method). This material was administered to 6 pregnant albino rats by gastric intubation in daily doses of 1 to 3 cc. during the last 2 weeks of gestation. Early pregnancy was determined by daily vaginal smears. Seven pregnant rats received normal gastric juice which had been heated over boiling water for 20 minutes, and 6 pregnant rats received normal gastric juice which was neutralized with concentrated sodium hydroxide immediately preceding administration. Gastric juice lacking free hydrochloric acid, obtained from patients with functional dyspepsia, hypochromic microcytic anemia, gall bladder disease, and other conditions, was given to 9 pregnant rats. Six pregnant rats received gastric juice obtained from patients having pernicious anemia and 3 pregnant rats were treated with gastric juice from patients suffering with carcinoma of the stomach. Thirteen untreated pregnant rats served as controls. An abundant supply of the normal laboratory ration (23.4% protein content) was constantly available to all rats. The total of 50 rats gave birth to 362 offspring.

Samples of blood were obtained from the newborn rats by cardiac puncture within a few hours after birth. The total number of erythrocytes per cubic millimeter of blood was determined by counting two samples from a standard pipet in a Neubauer ruled counting chamber. The volume of packed red cells per 100 cc. of blood was determined with the aid of van Allen hematocrit tubes. The mean corpuscular volume was calculated according to the method of Wintrobe.<sup>20</sup> Heparin was used as the anticoagulant. The mean erythrocyte diameter was determined by direct measurement of 50 cells on photographs of dry smears stained with Wright's stain and magnified 1500 times. Fields in which the blood cells were distorted or overlapping one another were avoided, and the attempt was made to measure only round cells. When a cell displayed only a slight tendency to oval shape, the greater diameter of the cell was measured. Stained smears were studied for the presence of nucleated erythrocytes and the number observed in counting 2000 erythrocytes was noted. The percentage of reticulocytes present was determined by recording the number observed while counting 500 erythrocytes on smears made after mixing a drop of blood with aqueous brilliant cresyl blue and counterstaining with Wright's stain. Probable errors were computed for all values determined.



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**Results.** The blood values of the 362 newborn rats are shown (Table 1). It will be seen that the average values of the blood of offspring of mothers which received heated normal gastric juice or gastric juice of patients having pernicious anemia were quite similar to such values of the blood of offspring born to untreated mothers. The mean values in the blood of offspring of mothers which received normal or neutralized normal gastric juice or gastric juice removed from patients with carcinoma differ significantly from the values just mentioned. The total number of erythrocytes of this group exceeds 3,000,000 per cubic millimeter. The hematocrit values remaining unchanged, the mean corpuscular volumes were lowered to the vicinity of 145 cubic microns. The mean cell diameters were smaller by  $0.5\mu$  or more than those of the other group. In between the values of these two groups were the values observed on offspring whose mothers had received the achlorhydric gastric juice. The percentage of reticulated and of nucleated cells present was subject to considerable variation in all groups and showed no essential relation to any of the other changes noted.

TABLE 1.—MEAN BLOOD VALUES OF NEWBORN RATS.

Type of gastric juice administered to mother during pregnancy.	No. of newborn rats.	Erythrocytes, millions per c.mm.	Packed red cells, cc. per 100 cc.	Corpuscular volume, cu. $\mu$	Reticulo-cytes, %.	Normoblasts, %.	Erythrocyte diameter, $\mu$ .
None (untreated controls)	92	$2.93 \pm 0.02$	$45.1 \pm 0.24$	$153.6 \pm 0.98$	$88.9 \pm 0.69$	$0.22 \pm 0.01$	$9.73 \pm 0.02$
Heated normal gastric juice	51	$2.83 \pm 0.03$	$43.7 \pm 0.20$	$154.6 \pm 0.85$	$91.7 \pm 0.74$	$0.20 \pm 0.01$	$9.60 \pm 0.03$
Gastric juice from patients having pernicious anemia	43	$2.83 \pm 0.03$	$44.5 \pm 0.46$	$157.3 \pm 1.03$	$91.9 \pm 0.74$	$0.22 \pm 0.02$	$9.60 \pm 0.04$
Normal gastric juice	49	$3.15 \pm 0.04$	$45.7 \pm 0.37$	$145.1 \pm 1.21$	$89.6 \pm 0.64$	$0.20 \pm 0.02$	$9.13 \pm 0.03$
Neutralized normal gastric juice	43	$3.24 \pm 0.03$	$46.5 \pm 0.38$	$143.9 \pm 1.11$	$95.1 \pm 0.57$	$0.21 \pm 0.02$	$8.94 \pm 0.03$
Achlorhydric gastric juice	62	$3.00 \pm 0.03$	$43.6 \pm 0.32$	$146.2 \pm 1.10$	$86.7 \pm 1.14$	$0.24 \pm 0.01$	$9.19 \pm 0.05$
Gastric juice from patients having gastric carcinoma	22	$3.41 \pm 0.05$	$48.0 \pm 0.57$	$141.1 \pm 1.72$	$91.4 \pm 1.33$	$0.14 \pm 0.01$	$9.07 \pm 0.05$

Although the differences in the mean cell diameters of the various groups were definite, these figures give but an incomplete picture of the actual changes which were observed in the erythrocytes as seen in dry smears. A more complete and graphic basis for comparison is obtained by the construction of Price-Jones curves. In Chart 1 such graphs for the blood of newborn rats whose mothers had received normal and heated normal gastric juice are compared with a similar curve of the newborn of untreated controls. The curve depicting the distribution in the "heated" group is essentially identical to that of the "control" group, whereas the curve depicting changes induced by the normal gastric juice is shifted to the left toward the smaller diameters.

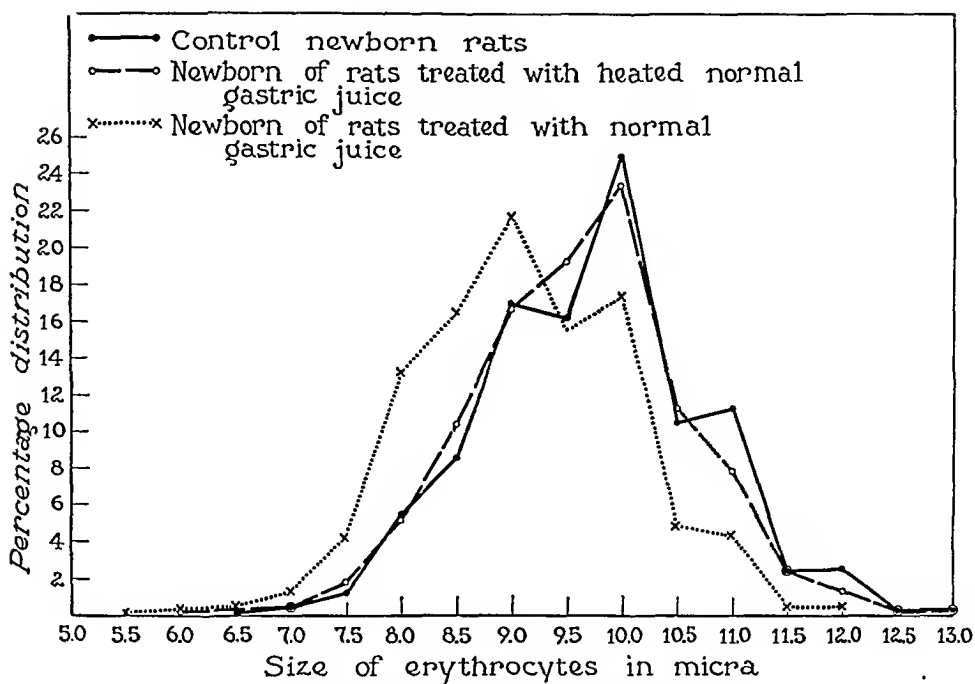


CHART 1.—Mean Price-Jones curve for blood of group of newborn rats whose mothers were treated with heated normal gastric juice and of group whose mothers received normal gastric juice compared with mean curve of control group of newborn rats whose mothers received no treatment during pregnancy.

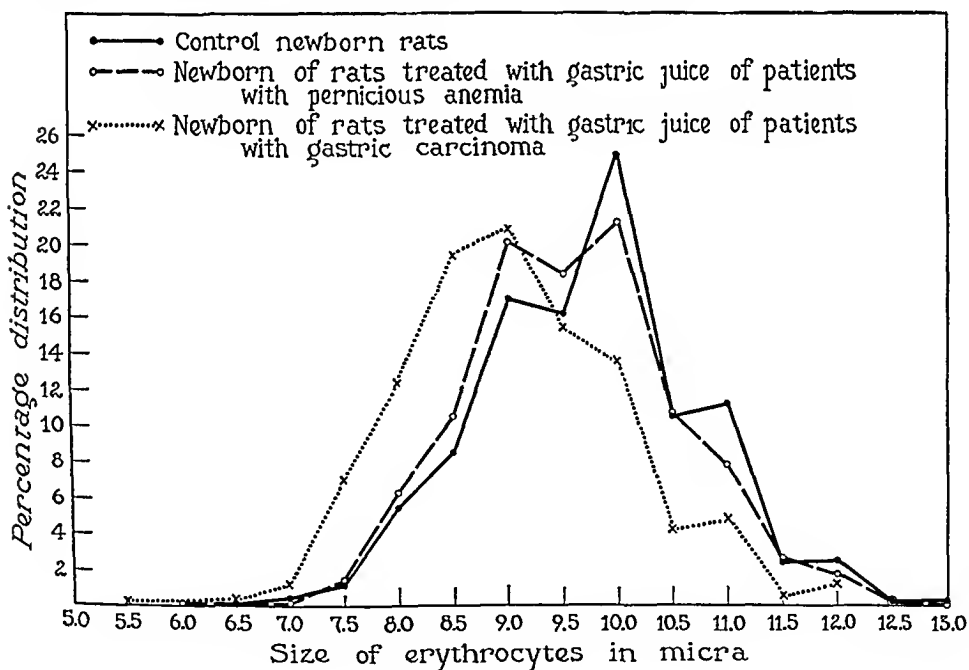


CHART 2.—Mean Price-Jones curve for blood of group of newborn rats whose mothers were treated with gastric juice of patients having pernicious anemia and of group whose mothers received gastric juice from patients having carcinoma of the stomach compared with mean curve of control group

In Chart 2 the curve of distribution of red cell diameters of the newborn of mothers receiving the pernicious anemia gastric juice is quite similar to that of the control group; whereas a similar curve for the carcinoma gastric juice lies considerably to the left, in the direction of smaller red cell diameters. The curve for the neutralized normal gastric juice was quite far to the left of that showing the control distribution (Chart 3); whereas the curve for the achlorhydric gastric juice occupies a position intermediate between the two.

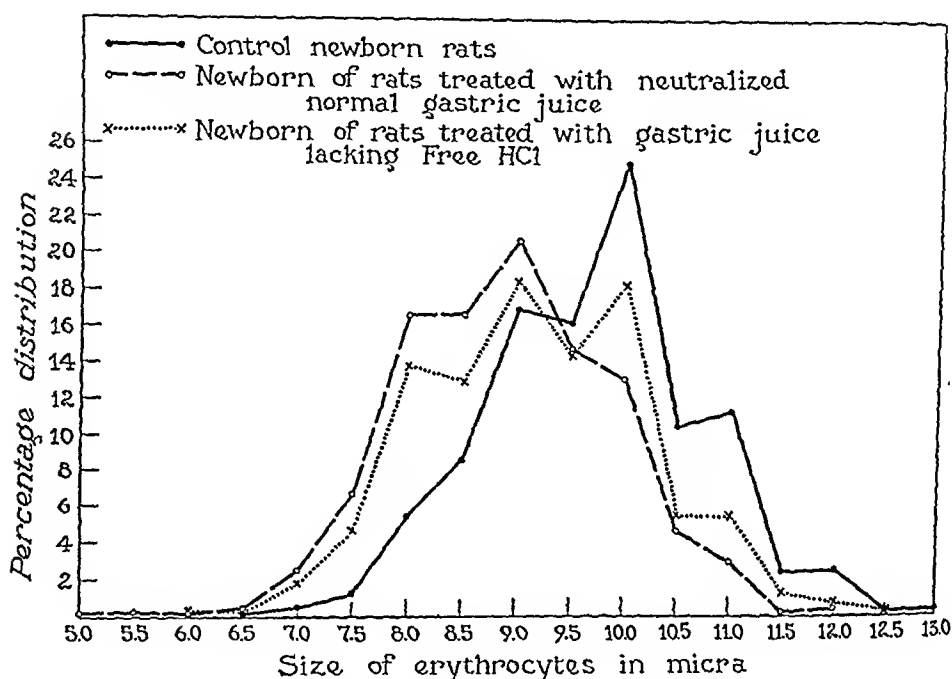


CHART 3.—Mean Price-Jones curve for blood of group of newborn rats whose mothers were treated with neutralized normal gastric juice and of group whose mothers received gastric juice from patients with achlorhydria compared with mean curve of control group.

These relationships are numerically expressed in Table 2. Here the range of erythrocyte diameter of the controls, 6.5 to 13 $\mu$ , is divided into three approximately equal divisions. The percentage of all cells falling into each of these three divisions is indicated for each of the various groups of animals studied. It will be noted in the table that the relative proportion of smaller cells is very much higher in the groups of newborn whose mothers had received normal or neutralized gastric juice, or gastric juice of patients with carcinoma of the stomach or simple achlorhydria, than in those constituting either the "control," the "heated" or the "pernicious anemia" group.

When individual determinations, rather than means, are considered, marked variations and overlappings of the data are noted for

all the values. Variations occur not only between individuals in different groups but between individuals in the same group and even in the same litter. Moreover, even means of litters within the same group exhibit variations and it is only when the means for a large number of litters (or individuals) are considered that trends can be definitely discerned. No correlation could be detected between any blood values of the newborn and the size of litters or the degree of maternal anemia.

TABLE 2.—DISTRIBUTION OF ERYTHROCYTES ACCORDING TO DIAMETERS.

(Control Range =  $6.50\mu$  to  $13.00\mu$ , divided into three approximately equal divisions.)

Type of gastric juice administered to mother.	% measuring less than $8.50\mu$ .	% measuring between $8.50\mu$ and $10.50\mu$ .	% measuring more than $10.50\mu$ .
None (untreated) . . . . .	7.15	76.81	16.04
Heated normal gastric juice . . .	7.73	80.47	11.80
Gastric juice of patients having pernicious anemia . . . . .	8.00	78.54	13.46
Normal gastric juice . . . . .	18.88	75.65	5.47
Gastric juice of patients with gastric carcinoma . . . . .	20.72	72.63	6.65
Achlorhydric gastric juice . . .	20.87	71.55	7.58
Neutralized normal gastric juice . .	26.48	69.91	3.61

**Comment.** In considering the differences in the assembled data of the blood of newborn rats whose mothers had received the various substances, two questions arise: 1, Are the changes significant? 2, What explanation may be found for these changes?

The answer to the first question depends on a number of factors. Since the differences noted were small, the first consideration must be the accuracy of the methods employed in arriving at the values recorded. Certainly the differences are too small to exceed the limits of experimental errors and individual variation in a single, or small number of determinations, even when experience, care in technique and consistency of method have reduced error to a minimum. Only on the basis of a large number of observations can these differences assume any importance. Since all but one of the groups of newborn rats, from which blood samples were taken, contained between 40 and 90 animals, it would seem that the requirement in numbers necessary to establish the significance of the results has been met. It must be understood that the changes reported here represent variations in means of recorded data, thereby indicating general trends, but do not represent changes which consistently may be reproduced to an equal degree in any individual.

Stasney, Higgins and Mann<sup>15</sup> expressed the opinion that the increase in the number of circulating erythrocytes associated with a decrease in their volumes and diameters observed in the blood of newborn rats whose mothers had received normal human or swine gastric juice intraperitoneally represented an acceleration of erythrocyte maturation which was induced by some substance present

in the concentrated gastric juice. Jones emphasized the fact that the changes in fetal blood which he observed in his studies did not indicate transformation of primitive erythroblasts of the pre-hepatic period into normoblasts or definitive red blood cells, but a speeding of their maturation toward primitive erythrocytes. It is generally accepted that such changes, occurring in the blood of a patient with pernicious anemia following the oral administration of normal gastric juice (with suitable opportunity for contact with a source of "extrinsic factor"), represent an acceleration of maturation. Restoration of normal red cell maturation then follows. Whether these changes observed in the blood of the rat fetus are at all comparable and the result of an availability of larger supplies of antianemic material provided by the administration of gastric juice to the mother cannot definitely be stated.

The administration of gastric juice by intubation was considered a more physiologic method than administration by injection. If the changes described by Stasney and his coworkers were due to the antianemic factor in gastric juice, such changes should also appear when the materials were given orally, providing of course that ample opportunity was afforded for contact with an abundant source of "extrinsic factor." This opportunity was provided and changes in the blood similar to those which Stasney and his coworkers described were obtained.

If one accepts the explanation offered by Stasney and his coworkers and the hypothesis of Castle,<sup>4,5</sup> a ready hypothesis is then at hand to explain these results. Normal gastric juice provides an excess of "intrinsic factor" which after contact with "extrinsic factor" of the diet may result in the production of an excess of antianemic principle in the pregnant rat. This would overcome the relative deficiency of this principle resulting from the burden of fetal hemopoiesis. Accordingly, more of the antianemic material would be available to the fetus and fetal hemopoiesis would be thereby enhanced. As the criterion of increased maturity we find in the blood of the newborn whose mothers received normal gastric juice a 7.51% increase in the number of circulating erythrocytes, a 5.53% reduction in the mean corpuscular volume, and a 6.16% decrease in the mean erythrocyte diameter.

The material in gastric juice which produces these changes in the blood of newborn rats bears resemblance to the "intrinsic factor" in some of its properties and distribution. The effectiveness of both is destroyed by heating. Castle and his coworkers<sup>6</sup> concluded that an acid environment inhibited the activity of the "intrinsic factor." Neutralization of the normal juice here employed seemed to enhance its activity. "Intrinsic factor" is lacking from the gastric juice of patients with pernicious anemia, or at least greatly reduced in amount. Gastric juice obtained from such patients was without effect on the blood picture of newborn rats.

The variable results obtained with gastric juice from patients with simple achlorhydria and gastric carcinoma are comparable to the results obtained by Hartfall and Witts<sup>9</sup> in their clinical studies with achlorhydric gastric juice. They concluded that the amount of antianemic material present in achlorhydric juice was always less than normal and subject to considerable variation. Several of the litters born to rats given such gastric juice samples showed no effect on the fetal blood cells.

Whether the material which produced the changes herein described is the "intrinsic factor," or whether the same factors govern hemopoiesis in the rat as in man, cannot be ascertained from the work at hand. In fact it has not even been established that these changes represent accelerated maturation. The various treatments administered were entirely without effect on the relative number of reticulated and nucleated red cells. Accordingly, if one thinks of maturation in terms of individual cells, there has been no progression of the cell toward a more mature type. The increase in number and decrease in volume and diameter would then have to be explained as the result of the premature appearance of later generations of erythrocytes, presumably from the fetal bone marrow which had been subjected to stimulation. This, of course, is actually maturation in a broader sense.

**Summary.** The normal blood values of the newborn albino rat have been determined for the conditions and technique of this study. Normal human gastric juice has been found to contain a substance which when administered orally to pregnant albino rats produces in the blood of the fetus a significant increase in the number of circulating erythrocytes and a decrease in their volume and diameter which can be detected at birth. This substance is without effect on the relative number of reticulated or nucleated red cells in the blood of the fetus. Its activity is enhanced by neutralization and destroyed by heating. The substance is absent from the gastric juice of patients having pernicious anemia. It is present in variable amounts in the gastric juice of patients with simple achlorhydria or carcinoma of the stomach. The possible relation of this substance to the intrinsic factor of Castle has been considered.

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## HEMOLYSINIC ANEMIA AND HEPATIC DEGENERATION CURED BY SPLENECTOMY.

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A CASE of hemolytic anemia showing clinical, metabolic and histopathologic evidences of impaired liver function is presented. A hemolysin was demonstrable in the blood serum prior to splenectomy, which was performed as an emergency measure because blood transfusions had aggravated the hemolysis and the liver dysfunction. Restoration of liver function and health and disappearance of the hemolysin followed the operation.

**Case Report.** P. A., a 17-year-old Jewish boy, was admitted to the Medical Service on April 18, 1939, and discharged on May 29, 1939.

**Present Illness.** The patient was in good health until March of 1937 when he was seized with chills and began to perspire profusely. The following morning jaundice of the skin and sclerae was noticed which became progressively deeper for 2 weeks and was associated with weakness, malaise, severe anorexia (especially for meat), nausea and occasional vomiting of bile-stained material. His skin did not itch; his urine was of dark color and his feces of normal, dark color. The jaundice gradually subsided; the patient returned to school and participated in athletics. However, examination at the Northern Liberties Hospital in May, 1937, showed the following: slight icterus, mild fever, slight leukocytosis and elevation of the icterus index. Roentgen ray examination at this time revealed a large gall bladder which emptied well after a fat meal without evidence of stones and a normal gastro-intestinal tract except for an irritable colon.

In August, 1938, an episode similar to that of March, 1937, occurred which lasted for 3 weeks. On April 1, 1939, weakness, malaise, anorexia and jaundice developed.

**Past and Family History.** The patient's general health had been excellent except for measles, pertussis and a myringotomy for otitis media in childhood. No other instances of jaundice appear in the family history.

**Physical Examination.** Temperature 100° F., pulse 96, blood pressure 130 systolic and 88 diastolic, weight 147 pounds, height 67½ inches. The

patient was comfortable. The skin and visible mucosal surfaces were intensely icteric and pale. A soft systolic murmur was heard over the entire precordium. The liver edge could not be palpated. The rounded, firm, smooth edge of the spleen extended 6 cm. below the costal margin in the left anterior axillary line and moved with respiration. No abnormalities were observed in the ocular fundi or in the remainder of the physical examination.

*Laboratory and Special Examinations.* Hemoglobin, 5.8 gm. (Haden-Hauser) per 100 cc.; erythrocytes 2,450,000 per c.mm.; leukocytes 8150; differential count—neutrophils 62% (non-filamented forms 9%, filamented 53%), lymphocytes 33%, monocytes 5%, normoblasts, 6 per 100 leukocytes; reticulocytes 4.3%; platelets 197,000 per c.mm.; icterus index 80 units, serum bilirubin 7.5 mg. per 100 cc., van den Bergh reaction indirect; bleeding time, 1 minute, coagulation time,  $3\frac{1}{2}$  minutes, prothrombin time (Howell's method), normal; fragility test—0.44% to 0.36% sodium chloride solution (identical with the control test); mean corpuscular diameter—8.02 microns with the following distribution: less than 7.5 microns, 19.4%, equal to 7.5 microns, 32.2%, greater than 7.5 microns, 48.4%. The erythrocytes varied in size from 3.75 to 12 microns and the Price-Jones curve was a biapical type with peaks at 7.5 and 9 microns. These measurements were repeated with similar results and the erythrocyte fragility was normal on two other occasions. On the stained blood film, the red blood cells showed marked anisocytosis, poikilocytosis and polychromatophilia, but small, darkly-stained erythrocytes (microspherocytes) were not seen. The blood Wassermann and Kahn reactions, fasting sugar, urea nitrogen, chlorides, serum protein (and albumin/globulin ratio), phosphatase, cholesterol and cholesterol esters (Table 1) were all within normal limits. The

TABLE 1.—CHEMICAL VALUES BEFORE AND AFTER SPLENECTOMY.

Date, 1939:	April.		May.				
	20.	22-26.	3.	5.	8.	23.	22-26.
Serum cholesterol:			SPLENECTOMY				
Total, mg./100 cc. . . . .	122	...		122	..	104	
Esters, mg./100 cc. . . . .	68	...		34	..	61	
Esters, % of total . . . . .	56	...		27	..	59	
Urobilinogen excretion, mg./24 hrs.:			SPLENECTOMY				
Feces . . . . .	..	502.0		..	..	..	51.9
Urine . . . . .	..	4.84		..	..	..	1.9
Serum protein, gm./100 cc. . . . .	7.0	...		..	5.1	6.2	

urine contained 4.84 mg. of urobilinogen per 24 hours<sup>25a</sup> but no bile pigment, bile acid salts, albumin, sugar, casts or red blood cells. The fecal urobilinogen\* excretion averaged 502 mg. per 24 hours on the analysis of a 4-day stool specimen. Repeated aerobic and anaerobic blood cultures were sterile. The blood group was B (Type III Moss). The stools contained no fresh or occult blood, ova or parasites. No malarial or other parasites were ever seen in the blood films. The electrocardiogram was normal. Biliary drainage, with two magnesium sulphate stimulations, revealed: B bile, 30 cc.; B-C bile, 140 cc.; microscopically, cholesterol crystals, black pigment and shaggy mucus strands. The fasting gastric juice contained

\* Urobilinogen determinations were conducted by R. H. Hamilton, Ph.D., M.D., of our Department of Biochemistry.



15 degrees of free acid. Radiographs of the skeleton revealed none of the changes occasionally observed<sup>3</sup> in the chronic hemolytic anemias and stones were not visualized in a flat plate of the abdomen.

*Clinical Course.* During the first week in the hospital the maximum daily temperature remained at 100° F. and the patient was comfortable. Since microspherocytosis and decreased resistance of the erythrocytes to hypotonic saline solution were not found, in a patient whose large family had no history of icterus, treatment with repeated blood transfusions seemed indicated rather than splenectomy.<sup>24</sup> Before transfusions were started the temperature began to increase and marked weakness, severe anorexia and vomiting developed. The course of the temperature, blood hemoglobin, red blood cell and serum bilirubin levels is shown in Chart 1. About 2000 cc.

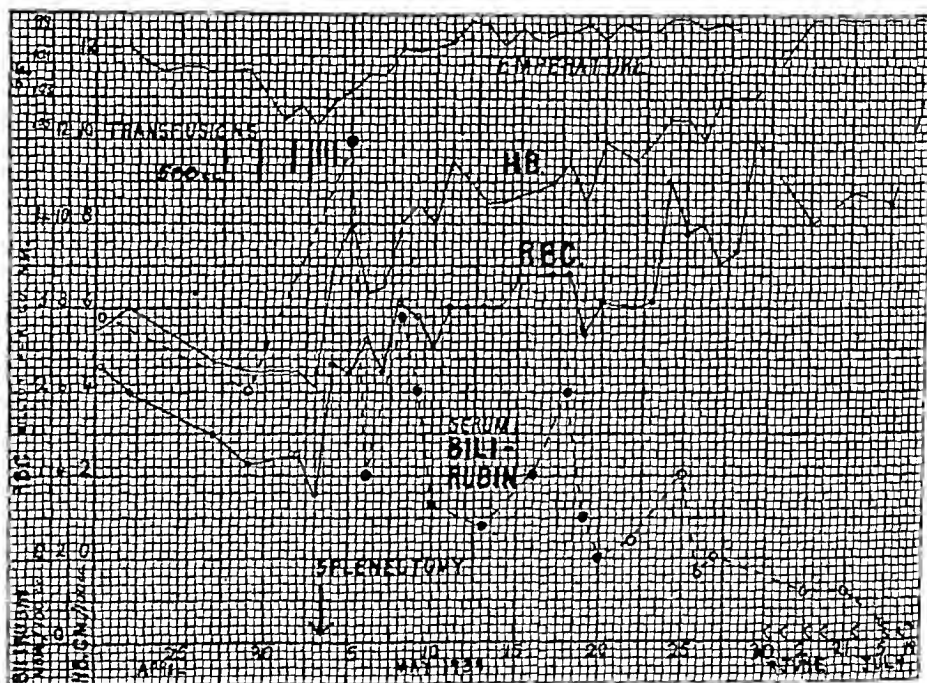


CHART 1.—Course of temperature, hemoglobin and red blood cell levels and serum bilirubin concentration. On the bilirubin curve the large, open circles indicate the indirect type of van den Bergh reaction; the large dots represent the direct type of reaction. The dates and the amounts of the transfusions are indicated.

of group B citrated blood was administered during a 5-day period (Chart 1) without untoward reaction except for a non-productive cough associated only with the first two transfusions. The cells and serum of the several donors were carefully cross-matched with the patient's cells and serum and with each other's cells and serum.

The progressive decrease in the erythrocyte and hemoglobin levels and the increasing icterus index indicated that the rate of hemolysis was increasing rapidly. On the morning of May 3d, the patient was intensely jaundiced with an icterus index of 200 units; the red blood cell count had decreased to 780,000 per c. mm.; the rectal temperature was 105° F.; the pulse rate was 160 per minute; the blood pressure was 90 systolic and 50 diastolic; the patient was delirious and unable to retain anything by mouth. The liver edge was palpable 2.5 cm. below the costal cage in the right mid-

clavicular line while the spleen remained at 6 cm. Multiple retinal hemorrhages had appeared. Bilirubin and albumin were found in the urine but there were no casts or erythrocytes in the sediment and tests for acetone and diacetic acid were negative. There was no significant acidosis (blood carbon dioxide combining power 49 vol. %) or nitrogen retention (blood non-protein nitrogen 29 mg. per 100 cc.).

In view of the failure to respond to transfusions and the desperate nature of the hemolytic crisis, emergency splenectomy offered the only hope of survival.<sup>10</sup> Under spinal anesthesia with 170 mg. of procaine, the spleen was quickly removed and a piece of the liver was excised for a biopsy (operation by W. E. B.). The spleen was enlarged and congested; the vessels of the pedicle were only slightly larger than usual; no adhesions were found. The liver extended 5 cm. below the costal margin and was of normal consistency and brown color with a slight bile stain. The gall bladder showed no thickening, emptied well on pressure and contained a stone about 2 to 3 mm. in diameter which was not removed. Within 2 minutes following ligation of the splenic pedicle, the systolic blood pressure rose from 90 to 120 and the pulse rate fell from 170 to 130 with a marked improvement in the volume of the pulse. Epinephrine was not employed either before or during the operation. A transfusion of 300 cc. of citrated Group B blood was given during the operation and an additional 700 cc. during the ensuing night using the same donors employed for the first two transfusions; no more transfusions have been given. The immediate post-operative condition was remarkably better than the preoperative state.

The postoperative course was clinically uneventful, except for blurred vision, related to the retinal hemorrhages, and for edema, associated with intravenous saline and glucose infusions and a decrease of the total blood serum protein level to 5.1 gm. per 100 cc. Postoperatively, the blood showed marked erythrocyte regeneration—increased macrocytosis (mean corpuscular diameter 8.8 microns on the fifth day), nucleated red blood cells (maximum of 31,000 per c.mm. on the third day), macro- and micro-normoblasts in mitosis (no megaloblasts), Howell-Jolly bodies and nuclear extrusion bodies—associated with neutropenia (minimum of 1180 filamented neutrophils per c.mm. on the second day), myelocytes (maximum of 87 per c.mm. on the fourth day) and thrombocytopenia (minimum of 58,000 per c.mm. on the sixth day). The temperature, pulse, symptomatology, erythrocyte count, hemoglobin level and icterus improved rapidly (Chart 1). The effect of supportive therapy during the critical pre- and postoperative days with intravenous glucose and physiologic saline solutions, insulin, thiamin chloride, liver extract (pernicious anemia type), yellow bone marrow extract, vitamin K (Klotogen), bile acid salts, dilaudid and prostigmine cannot be evaluated.

Less than 4 weeks after splenectomy, the patient was able to walk about all day without fatigue; the icterus had almost entirely disappeared and there was no pallor. The retinal hemorrhages were absorbing. Body weight had decreased to 131 pounds. Special laboratory studies repeated during the last week in the hospital showed: fecal urobilinogen 51.9 mg. per 24 hours; urinary urobilinogen 1.9 mg. per 24 hours; normal serum cholesterol, cholesterol esters and total protein levels (Table 1); normal blood urea nitrogen concentration; no occult blood in the urine; no hemoglobinuria (spectroscopically); in the biliary drainage: 40 cc. of B bile, 120 cc. of C bile, macroscopic amounts of calcium bilirubin pigment, but no cholesterol crystals microscopically; in the Roentgen ray examination of the gall bladder with tetraiodophenolphthalein: poor concentration of the dye but good contraction after the fat meal and no evidences of stones.

Eleven weeks after the splenectomy the patient reported that he had been living an entirely normal life and was gaining weight (160 pounds).

Icterus of the sclerae was no longer detectable; the liver edge was just palpable at the costal margin on deep inspiration; there were no abnormal physical findings except the absorbing retinal hemorrhages. Examination of the blood showed: erythrocytes 5.45 million per c.mm.; hemoglobin 13 gm. per 100 cc.; mean corpuscular diameter 7.9 microns with a range of 4.5 to 10.5 microns and the following distribution: less than 7.5 microns, 12% equal to 7.5 microns, 40.4%, greater than 7.5 microns, 47.6% and a monopical Price-Jones curve; leukocytes 7700 per c.mm. with a relative lymphocytosis in the differential leukocyte count. Four months after the operation and after a camping trip in the mountains the patient was in fine condition, he was no longer conscious of blurred vision; the blood hemoglobin was 16.5 gm. per 100 cc. and the erythrocyte count was 5.64 million per c. mm.

**Pathologic Anatomy.\*** The spleen measures 22 by 15 by 12 cm. and weighs 1000 gm.; its capsule is smooth and rather tense; it is firm; the follicles are not distinguishable. Microscopically (Fig. 1) there is a remarkable hyperplasia of the reticulum; numerous areas are made up entirely of reticulum cells with the exclusion of lymphocytes. There is much evidence of a rapid red blood cell destruction; most of the red cells showing a vague, smudged outline and there is considerable fresh and old blood pigment. Erythrophagocytosis is not seen. There is a diffuse infiltration with neutrophils. The lymphoid follicles are few in number, rather poorly demarcated and show an underdevelopment of the secondary follicles. The sinuses are not abnormal. The specially stained contact preparations of the spleen show young forms of both erythrocytes and granulocytes indicating myelogenous metaplasia. Thus the picture is one of reticulum hyperplasia and hemopoiesis of the spleen with increased red cell destruction.

It should be emphasized that this histopathology is not characteristic of the spleen in congenital hemolytic jaundice<sup>16</sup> but resembles that reported by Israëls and Wilkinson<sup>14</sup> in 4 adults with acholuric jaundice.

Microscopic examination of the liver biopsy (Fig. 2) reveals a very marked fatty change. Well over one-half of the cells show huge vacuoles with destruction of almost the entire cell. The remaining cells show small globules of fat, bile pigment retention, and granular degeneration of the cytoplasm, the whole picture being one of degeneration. The portal areas show a striking infiltration with neutrophils. These take no special arrangement but are diffusely scattered throughout the portal areas. The majority of the biliary radicles are healthy in appearance.

**Serology.** A hemolysin was demonstrated *in vitro* in the patient's blood serum before splenectomy. In preliminary tests (B. M. West, B.S., Chief Technician), 3 cc. of the patient's fresh blood serum (April 25th) were mixed with 3 drops of a 10% suspension of the patient's unwashed erythrocytes in physiologic saline solution, as well as with similar suspensions representing each of the four normal blood groups, and incubated in open tubes at 37° C. over night (14 hours). Complete hemolysis of the patient's Group B cells, the specimen of normal Group B cells and partial hemolysis of the normal Group O cells occurred. The normal Group A and AB cells showed the agglutination to be expected in the patient's Group B serum. Samples of normal serum of each of the four blood groups were incubated in a similar manner with the patient's cells; no hemolysis occurred; agglutination appeared in the Group A and O sera. On April 27th, just before the first transfusion, fresh samples of the patient's serum and cells gave identical results. Autoagglutination of the patient's cells in his own serum was not observed but the hemolysis that always occurred may have masked the recognition of macroscopic agglutination. When a tube of the patient's coagulated blood (serum and clot in contact) was incubated, hemolysis was not detected macroscopically.

\* By E. E. Aegerter, M.D., of our Department of Pathology.

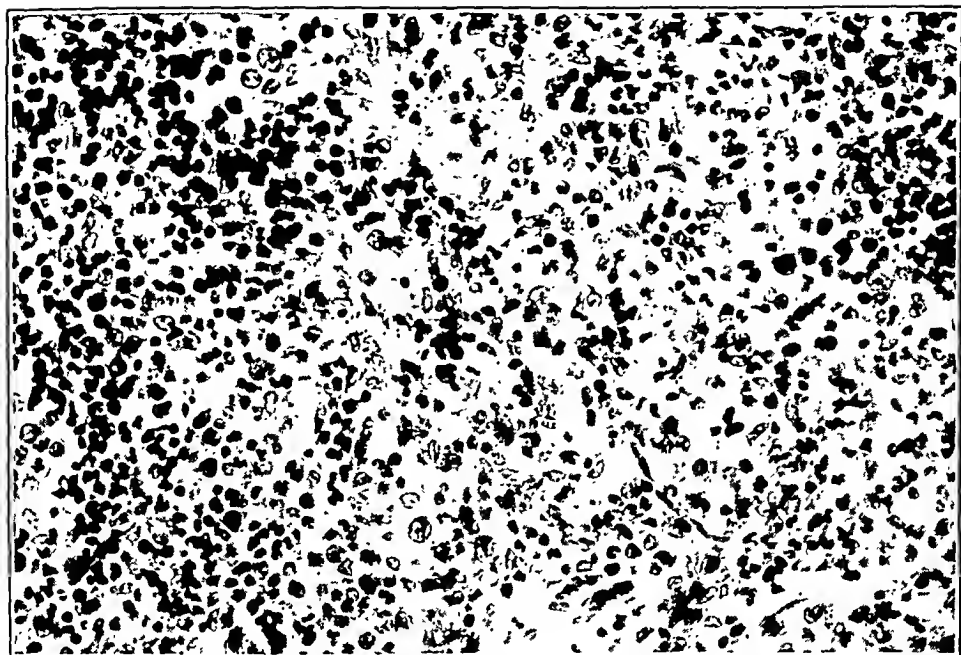


FIG. 1.—A section of the spleen with reticulum cell hyperplasia. There are numerous young forms of both red cells and myelogenous white cells. There is considerable old blood pigment. (300 $\times$ .)

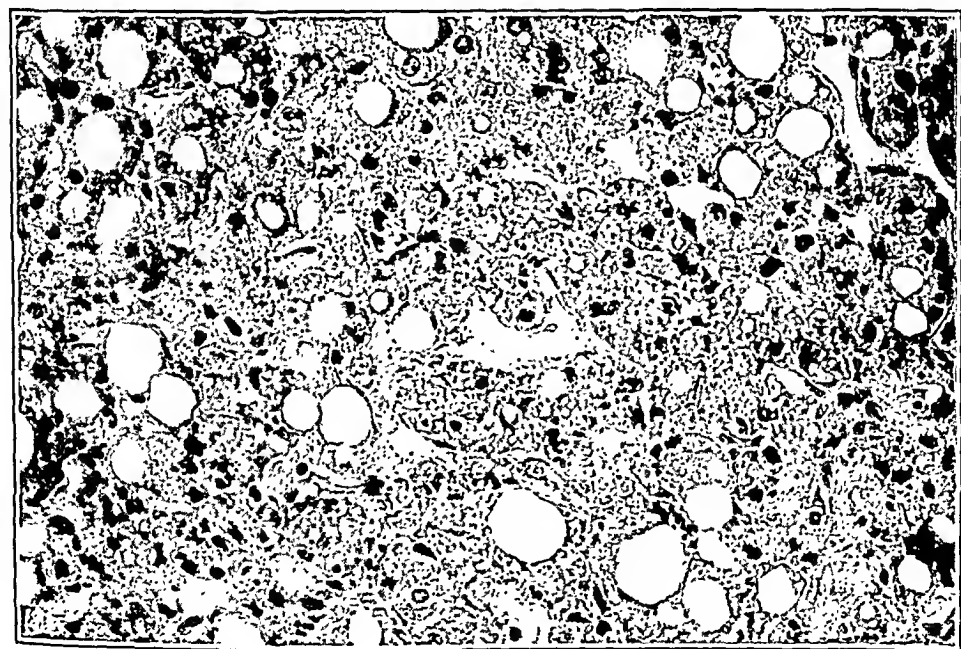


FIG. 2.—A section of the liver with cell degeneration prominent. There are intracellular fat vacuoles of varying sizes, pigment retention, swelling and granular degeneration of the liver cells and an infiltration with leukocytes. (400 $\times$ .)



On May 3d, just before the splenectomy, samples of the patient's serum and cells were obtained for a more detailed study\* of the serologic characteristics of this hemolysin. The reagents were prepared as follows: Erythrocytes: specimens of Groups AB, A, B and O cells and the patient's cells were washed three times with physiologic saline solution; suspensions containing 2% of cells were prepared; three different normal donors of each blood group were employed. Serum: one portion of the patient's serum was inactivated at 55° C. for 30 minutes; the other portion was used without heating; the patient's serum and cells had stood in the ice box for 48 hours before the first tests were carried out. Complement: a 1:10 dilution of fresh guinea pig serum in physiologic saline solution was used (the number of units of complement was not determined); fresh human sera of appropriate blood groups was also used with similar results. The procedure was carried out as follows: after mixing the reagents (red cell suspension 0.2 cc., serum 0.4 cc., complement 0.2 cc., saline 0.2 cc.) the tubes were incubated for 1 hour at 37° C.; after a preliminary reading, incubation was continued in the ice box over night.

*Observations.* 1. Uninactivated patient's serum, with or without added complement, showed marked hemolysis of normal Group A, B and O cells, slight hemolysis of Group AB cells, but no hemolysis of the patient's cells. 2. Inactivated patient's serum, without the addition of complement, showed no hemolytic action. 3. Inactivated patient's serum plus complement hemolyzed the patient's cells and the normal Groups AB and A cells in dilutions up to 1:16 but not in 1:24. 4. After standing in the ice box for 3 weeks the hemolytic titer of this preoperative serum decreased to a dilution of 1:8 both for the patient's postoperative cells and for fresh specimens of normal Groups AB and A cells. 5. When this 3 weeks' old serum was mixed with normal Group B serum and allowed to stand for 10 minutes at room temperature before the patient's postoperative cells and complement were added, hemolysis did not occur (in the 1:4 dilution of serum) during the usual incubation. 6. The patient's 3 weeks post-splenectomy, fresh or inactivated serum, without the addition of complement, did not hemolyze the patient's postoperative cells or the normal cells of Groups A, B or O; if complement was added, hemolysis of Group A cells occurred in a dilution of 1:16; normal Group AB cells were not tested. 7. The ice box incubation did not increase the degree of hemolysis over the amount present at the end of the 1 hour incubation at 37° C. in any of these tests. 8. Preliminary incubation in the ice box or at room temperature, before the 1 hour incubation at body temperature, did not alter the hemolytic action in any of these tests.

In summary, the hemolysin that was active against the patient's cells (a) required complement, (b) did not require cooling, (c) decreased in activity on standing in the ice box for 3 weeks, (d) was neutralized by normal homologous serum and (e) was active against the patient's 3 weeks post-splenectomy cells as well as the preoperative cells. This hemolysin was not present in the patient's serum 3 weeks after the splenectomy.

An uninactivated, sterile saline extract of minced splenic tissue incubated in the same manner with and without the addition of complement was actively hemolytic for normal cells of Groups A, B and O, slightly hemolytic for normal Group AB cells and not at all for the patient's B cells. This is identical with the peculiar hemolytic property of the patient's uninactivated preoperative serum that was removed by heating. Heat inactivation of the splenic extract resulted in the formation of a heavy precipitate; no hemolytic action was demonstrable in the supernatant fluid. Aërobic and anaërobic cultures of this spleen, made at the operating table, were sterile.

\* Conducted by E. H. Spaulding, Ph.D., of our Department of Bacteriology.

**Discussion.** The clinical condition of the patient, the biochemical evidences of impaired liver function and the histopathology of the liver indicate that this patient's severe crisis was due to an acute liver failure. The clinical evidences of impaired liver function were: anorexia succeeded by nausea and vomiting, vague epigastric discomfort, delirium, coma, fever, tachycardia, hypotension, increasing hepatomegaly and marked icterus. The laboratory evidences (Table 1) of liver dysfunction were: a decrease in the esterified portion<sup>11</sup> of the total serum cholesterol; an increase in the urinary urobilinogen excretion;<sup>25b</sup> the change of the van den Bergh reaction (Chart 1) from indirect to direct<sup>22</sup> without evidence of obstruction of the extra-hepatic biliary tract; the appearance of bile pigment in the urine at the height of the crisis; a decrease in the total blood serum protein concentration;<sup>12</sup> and the cholesterol crystals and black pigment in the biliary drainage material.

The rapid clinical and laboratory recovery of liver function in the face of such severe liver damage (Fig. 2) suggests that the spleen was responsible for the degeneration of the liver. The extensive fatty and pigmentary degeneration with peri-portal infiltration of neutrophils revealed in the liver biopsy does not appear in other types of severe anemia. Similar lesions have been reported at the autopsy of patients with hemolytic anemia.<sup>7,8,19</sup> Pigmentary degeneration of the liver with fatty degeneration of the parenchymal cells in the central portion of the liver lobule has been recognized in the chronic hemolytic anemias.<sup>1,20,22</sup> Fatal transfusion reactions produce scarcely any histologic liver damage in patients without preëxisting hemolytic anemia.<sup>9</sup> The frequency of severe clinical crises and the greater severity of the anemia characterize the acquired form of hemolytic icterus in contrast with the familial variety.<sup>17</sup> The observations on this patient indicate that an acute liver failure is one pathogenic mechanism of the clinical crises characteristic of the hemolytic anemias.

The rise of the red blood cell count from 780,000 to 2.6 million during the first 18 hours after splenectomy indicates that the spleen was responsible for the previously falling erythrocyte count and the increasing serum bilirubin concentration. In spite of the marked anemia prior to splenectomy, the small number of normoblasts and reticulocytes suggests that some factor inhibiting erythropoiesis,<sup>2,10</sup> as well as a hemolytic factor, was removed by the splenectomy. The marked normoblastic response and the transient neutropenia and thrombocytopenia following the operation likewise suggest that red blood cell formation had been depressed by some action of the spleen.

Pepper's<sup>21</sup> classification of the hemolytic anemias according to the mechanism of hemolysis may be rephrased as follows:

A. Familial. 1, Congenital hemolytic jaundice (spherocytosis); 2, sickle cell anemia.

B. Acquired. 1, Allergic (favism, drugs, etc.); 2, chemical (industrial exposure, drugs, etc.); 3, infectious (Strep. hemolyticus, bacillus Welchii, ? Lederer's acute hemolytic anemia, etc.); 4, infestations (malarial plasmodium, etc.); 5, physical (cold in paroxysmal hemoglobinuria); 6, symptomatic (leukemia, Hodgkin's disease, tuberculosis, etc.); 7, idiopathic (such as paroxysmal nocturnal hemoglobinuria); 8, the hemolysin anemia, first described by Chauffard and Vincent,<sup>4</sup> may be added to this classification.

This case of macrocytic, hemolytic anemia may be classified as a *hemolysin* anemia. Although there was chronic icterus and previous severe episodes of jaundice, there was no family history of jaundice and the red blood cells have shown neither increased fragility in hypotonic saline solution nor spherocytosis during 3 months of close observation. A hemolysin was present in the blood serum prior to splenectomy and the case resembles Cases 1 and 2 reported by Dameshek and Schwartz;<sup>6a</sup> the hemolysin is likewise similar.<sup>6b</sup> Krumbhaar<sup>17</sup> and Dameshek<sup>5</sup> have reviewed the previously reported cases of this type. The clinical response to splenectomy, the histopathology of the spleen and the disappearance of the hemolysin from the blood serum after splenectomy suggest that the spleen was responsible for the serum hemolysin, the hemolytic anemia and the liver damage.

In the hemolytic anemias, the primary diagnostic efforts should be directed toward a determination of the mechanism of hemolysis,<sup>21</sup> for in many of these types of hemolysis splenectomy is either not indicated or has proved of little or no value.<sup>24</sup> Having excluded the known causes of hemolysis and demonstrated a hemolysin in the blood serum, splenectomy is indicated to remove the organ which is causing the hemolysis and injury to the liver. In Lederer's acute hemolytic anemia, which is usually a macrocytic anemia, transfusions are adequate therapy.<sup>15,18</sup> However, transfusions must be used with caution in the hemolytic anemias because of the danger of aggravating the hemolysis. This danger has been emphasized by Sharpe and Davis<sup>23</sup> and is illustrated in this and many other cases.<sup>6a, 8, 10, 13</sup>

To clarify the problem of ictero-anemia, blood serum hemolysins should be searched for in all types of hemolytic anemia until adequate information on the nature and rôle of these antibodies is available. Dameshek and Schwartz<sup>6b</sup> believe that spherocytosis represents a milder rate or degree of the action of a serum hemolysin than the macrocytic type of hemolytic anemia such as was present in this case and in 2 of their cases.<sup>6</sup> Furthermore, Hill<sup>13</sup> has reported



that microspherocytosis was present only during some stages of the course of clinically typical cases of congenital hemolytic jaundice.

**Conclusions.** A case of *hemolytic* anemia showed a macrocytic type of anemia in its third critical episode during 2 years' time. Transfusions aggravated the anemia; the symptoms and laboratory evidences of severe liver dysfunction became apparent.

A hemolysin was demonstrable in the blood serum before but not after the splenectomy.

Splenectomy was performed successfully on a moribund patient as an emergency measure in the treatment of the hemolytic anemia and the acute liver failure.

The clinical, hematologic and biochemical response to splenectomy was astonishingly complete and rapid although the patient was shown by biopsy at the time of operation to have severe fatty and pigmentary degeneration of the liver.

[Hemolytic anemia, in the broad sense of the term, can have many causes and mechanisms. For instance, congenital hemolytic jaundice (of which the so-called acquired form is now regarded as merely the activation of a latent stage) appears to be due to a congenital defect of the erythrocyte (spherocytosis) that makes it more susceptible to rupture by osmotic change. In the present case, which obviously is not one of congenital hemolytic jaundice, a hemolysin was clearly demonstrated and the dramatically successful results of splenectomy showed either that the hemolysin was formed in the spleen or at least that the presence of the spleen was a requisite for the production of liver damage. Such cases are rare. It is possible, however, that careful serologic studies will show hemolysins in a greater proportion of cases. Some years ago, studying artificial plethora, we found that with repeated injections of blood, polycythemia was eventually replaced by anemia of increasing severity; and yet we were not able to demonstrate the hemolysins that we felt were probably present. Perhaps some of the clinical hemolytic anemias fall in a similar category. I am glad to comply with the authors' request to add this supplementary note.—ED.]

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**ERYTHROCYTE MORPHOLOGY IN EXPERIMENTAL HEMOLYTIC ANEMIA AS INDUCED BY SPECIFIC HEMOLYSIN.\*****By W. D. TIGERTT, M.D.,**

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BECAUSE of the interest aroused by the recent report of Dameshek and Schwartz<sup>4</sup> suggesting the relationship of human hemolytic anemias and the experimental hemolytic anemias produced in animals by injection of species-specific hemolytic serum, and because the data so obtained are comparable to certain types of blood pictures seen clinically, the results of this preliminary investigation of the subject are reported.

The study was undertaken in an attempt to establish a "standard" hematologic reaction in the dog following a single injection of anti-dog cell hemolysin. The findings will be utilized in future study as a basis of comparison or contrast in animals receiving hemolysin after some other alteration in erythrocyte dimensions or metabolism.

**Method.** *Preparation of Hemolysin.* Rabbits were given 5 intravenous injections of 1 cc. of 20% suspension of thrice washed dog red cells in normal saline at 3- or 4-day intervals. The animals were bled 7 days after the last injection.

*Titration.* To 0.5 cc. of progressive dilutions of the rabbit serum were added 0.5 cc. of a 2% suspension of washed dog cells, 1.5 cc. of 0.85% saline and 0.5 cc. of a 1 to 10 dilution of fresh guinea-pig serum. This was followed by incubation for 1 hour at 37° C. Lysin titers are expressed in terms of the final highest dilution at which definite hemolysis was visible. Titers as high as 1 to 9600 were obtained. Agglutinin titers, expressed in the same terms, were equal to or slightly higher than the respective hemolysin concentrations.

After inactivation at 56° C. for 30 minutes the sera were preserved undiluted by freezing.

*Production of Anemia.* Eleven mongrel dogs, on a diet of commercial dog biscuits, were given single intraperitoneal injections of varying amounts of hemolytic serum.

*Hematologic Methods.* Determinations were performed daily at the height of the anemia and at longer intervals thereafter. Blood was obtained from the ear vein except for hematocrit determinations. Blood was drawn from the cubital vein in a syringe coated with mineral oil for this determination. Heparin (Connaught) was used as an anticoagulant in the concentra-

\* This investigation was aided in part by a grant from the Fraser Fund, Baylor University College of Medicine.

tion of 2 units per cubic centimeter of blood. In 2 of the animals all determinations were carried out with heparinized blood.

Bureau of Standards red cell pipettes and counting chambers were used throughout, counting at least 10 squares after mechanical shaking of the pipettes. Hayem's solution was used as a diluent, frequently being checked with Gower's solution<sup>7</sup> if clumping of the red cells was marked. The majority of the counts were performed by one individual. Hemoglobin estimations were made by the Newcomer method. Wintrobe's hematocrit tubes<sup>15</sup> were used and were read after centrifugation for 1 hour at 3800 r.p.m.

Reticulocyte counts were made by the damp-chamber method using brilliant cresyl blue and counterstaining with Giemsa. Cell diameters were obtained by projection and direct measurement at a magnification of 3000 diameters. The slides used were stained with Leishman's and were counterstained with 1% aqueous eosin. At least 250 cells were counted for each determination and in some instances this was increased to 500. The average diameter and the standard deviation were calculated by the method of Price-Jones.<sup>12b</sup> Red cell thickness was estimated by the formula:

$$\text{mean corp. thickness} = \frac{\text{mean corp. vol.}}{3.14 \text{ rad.}_2}$$

Fragility tests were carried out according to the technique of Daland and Worthley.<sup>3</sup> Sparkman's method<sup>13</sup> was used for the urobilinogen determinations.

**Results. Normal Values.** The erythrocyte level of the animals used varied between 6.6 and 8 million cells per c.mm. (In 1, the initial blood count was 5.5 million.) Average hemoglobin values lay between 12.9 and 15.2 gm. The reticulocyte count was less than 1.5% in all instances.

The average cell diameter varied between 6.99 and 7.34 microns, with an average mean corpuscular volume of  $68 \pm 5$  cu. microns. The standard deviation of the diameter, counting 250 cells, was less than 0.5 micron. The calculated cell thickness averaged 1.85 microns.

Hemolysis usually began around 0.44% saline and was complete at 0.32%.

**Control Experiments.** The injection of amounts of normal rabbit serum comparable to the amount of hemolytic sera used was followed by no significant change in cell size and only a slight reticulocyte response.

**General Effects.** Following the injection of the hemolysin, certain changes were observed in all of the animals, varying in intensity with the amount and titer of the hemolysin. The earliest change that could be detected without cell measurements was a decreased resistance of the red cells to hemolysis by hypotonic saline. This was present after 4 to 12 hours, becoming more evident as cell destruction began and hemoglobinemia developed. With the development of hemoglobinemia the level of the red cells and hemoglobin began to decrease, usually reaching the lowest reading in 3 to 6 days. With larger amounts of hemolysin destruction of nearly all of the circulating erythrocytes was observed, with a cor-

responding lesser destruction with smaller amounts of lower titers. Examples of the levels of anemia produced are shown in Chart 1.

If the amount of hemolysin administered was large, death resulted at this stage. If smaller doses were given, the animal usually maintained the red cell level reached for 2 to 4 days, following which there was a gradual return of the red cell count and hemoglobin toward normal readings.

Prior to the rise in red cell count examination of the stained blood films showed definite signs of bone-marrow response. If the demand were only moderate, an increase in the number of reticulocytes was the only change. If the demand were more severe, nucleated red cell forms were frequent. Occasional megaloblasts were observed

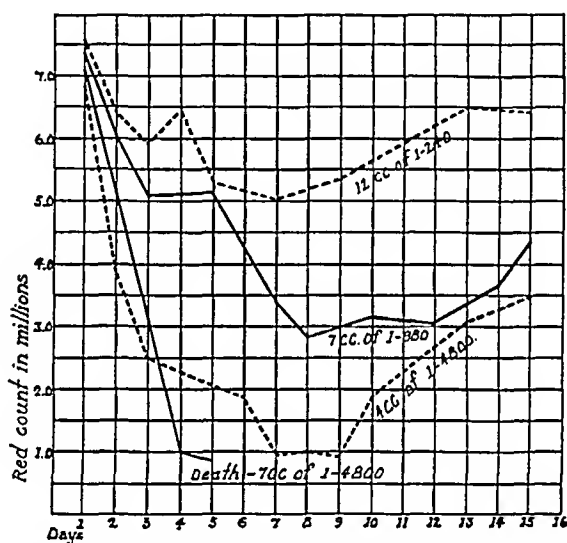


CHART 1.—The duration and severity of the depression in the erythrocyte level caused by a single injection of hemolysin. Each line represents a different animal.

in the most severe anemias, and a loss of phase between the nucleus and the cytoplasm of the erythroblasts and normoblasts was a common observation. The reticulocyte level occasionally reached 50% and numerous polychromatophilic cells were present in the recovery phase.

*Pigment Excretion.* With the exception of 1 animal, the hemoglobinemia was of sufficient degree to be accompanied by moderate or severe hemoglobinuria. The hemoglobinuria, once established, continued for several days, usually diminishing in amount and disappearing after the red cell count started to rise.

Stool urobilinogen excretion showed marked increases as the anemia progressed, with the highest readings obtained about 24 hours after the low level of the red cell count was reached. In

some instances the output was as high as 900 mg. per 100 gm. of stool (approximately 30 times the normal excretion).

*Hematocrit Readings.* During the first 3 to 5 days the volume of packed cells decreased in proportion to the drop in erythrocytes. At this stage, in some instances, hematocrit readings were inaccurate because of the varying amounts of cell debris present. Occasionally, on the third or fourth day a slight rise (3 to 4%) was noted, which was not associated with demonstrable cell debris. During the recovery phase a definite rise in the hematocrit levels as compared to the rise in red cell count was present, the amount varying directly with the immaturity of the cells. Mean corpuscular volumes of 126 and 123 cu. microns were the extremes recorded.

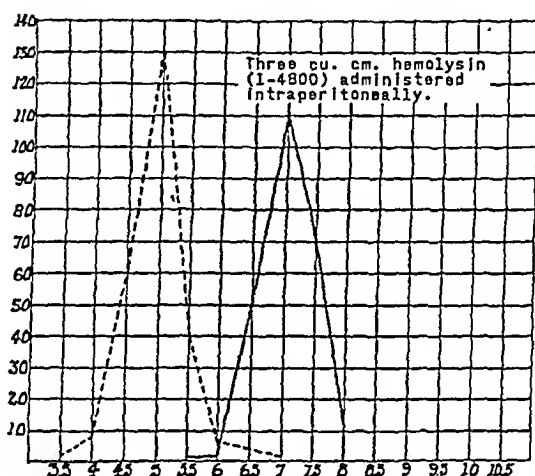


CHART 2.—Price-Jones curves illustrating extreme changes in cell diameter following a single injection of hemolysin. The solid line shows the normal curve; the dotted line, the curve obtained 2 days later. The standard deviation of both curves is less than 0.5.

*Erythrocyte Diameters.* Following the injection of a large amount of hemolysin there was observed a marked decrease in the diameter of the erythrocytes. This change was demonstrable in 12 hours, but usually reached the low level in about 48 hours. In 1 instance there was a drop from 7.2 to 4.9 microns (Chart 2), with proportionately smaller diminutions in diameter following smaller amounts or lower titers of injected hemolysin.

The standard deviation of this type of cell population closely approximated the normal standard deviation, or in some instances, was less than the normal standard deviation.

Usually on the third or fourth day there was observed a significant increase in the standard deviation associated with a widening of the base of the curve, due to the appearance of cells of normal size or larger. Within 2 or 3 more days the presence of two separate

cell components could be demonstrated, as shown by the bi-modal curves obtained (*i. e.*, two peaks in curve of cell diameters). It is significant to observe that in some instances the modes of the curves (as those shown in Chart 3, eighth day, and Chart 5, eleventh day) were separated by a distance greater than 3 times the standard deviation of the component of cells with decreased diameters.

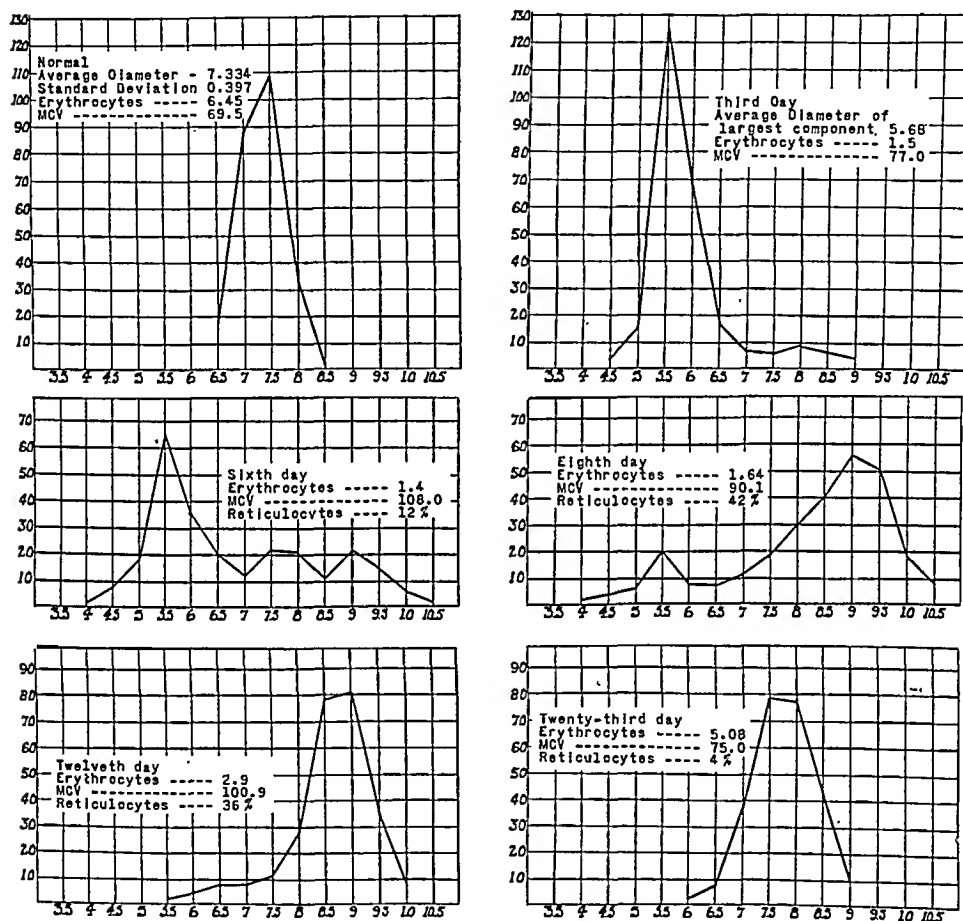


CHART 3.—Price-Jones curves illustrating the decrease in diameter of the circulating erythrocytes after a single injection of hemolysin, followed by gradual diminution in the number of these cells and their almost complete disappearance by the twelfth day. Note that the cells from the bone marrow are at first relatively normal in size but soon shift markedly toward larger cells following which the entire new cell population gradually shifts back toward normal size. Statement of the mean cell diameter in certain of these curves would give an entirely erroneous notion as to the type of cells present.

The further course of these bi-modal curves is of much interest. The cells of small diameter gradually decreased in number, occasionally seeming also to decrease in diameter (Chart 5), persisting in the blood stream for periods up to 1 month following injection

of the hemolysin (Chart 4). The length of survival of these cells was inversely proportional to the amount of hemolysin administered.

The other component of the curves, after small doses, consisted of cells of normal diameter or of only slightly increased diameter (Chart 4). With larger amounts of hemolysin the curve first was

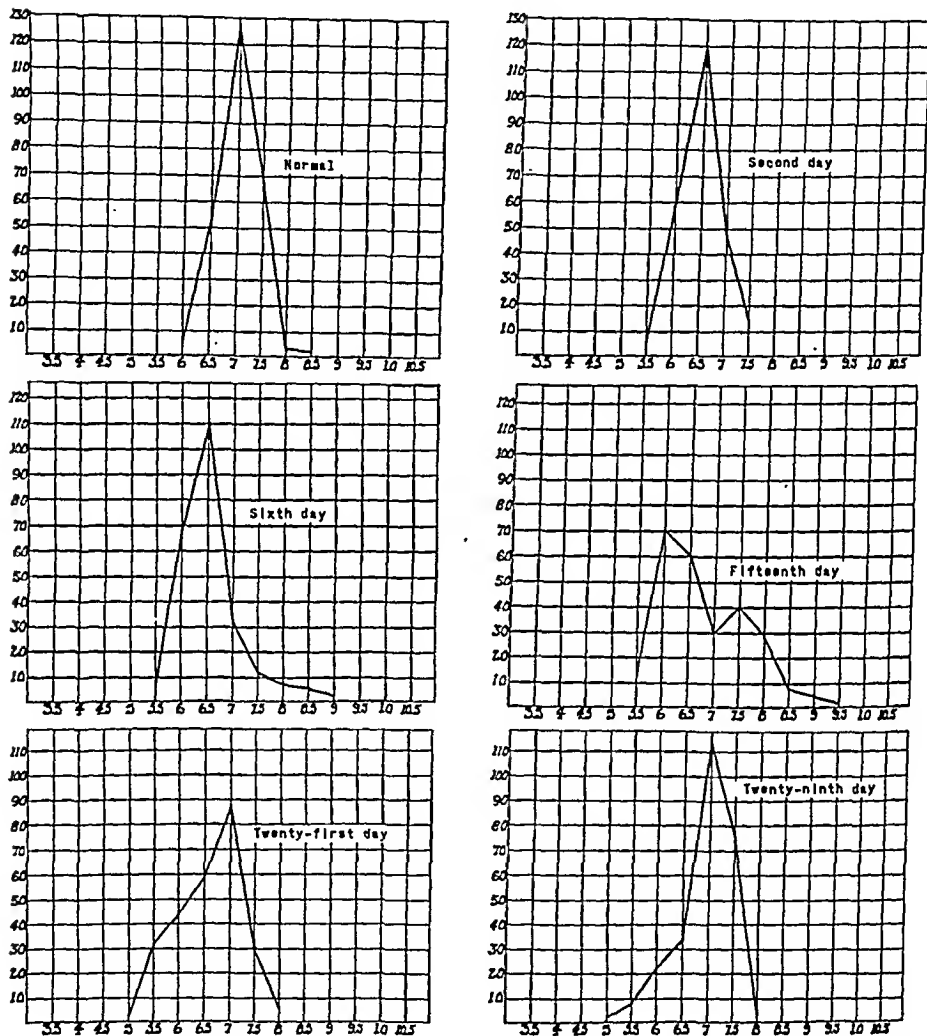


CHART 4—Price-Jones curves illustrating a slight decrease in diameter of the circulating cells with a response of nearly normal sized cells. Note that the left component persists in all of the curves shown and that the smaller cells in this component show a relative increase in number.

similar but soon shifted so that cells with large diameters formed its main component. As the blood count rose the group of large cells increased in number, and at the same time the average diameter tended to shift back toward normal figures, usually approaching normal in 3 to 4 weeks. In some instances, particularly following

small amounts of the hemolytic serum, there was only a slight decrease in the diameter of the circulating cells and the response was with cells of nearly normal diameter, so that the two components were more or less combined, forming a uni-modal curve with a broad base and a high standard deviation (Chart 4, twenty-first day).

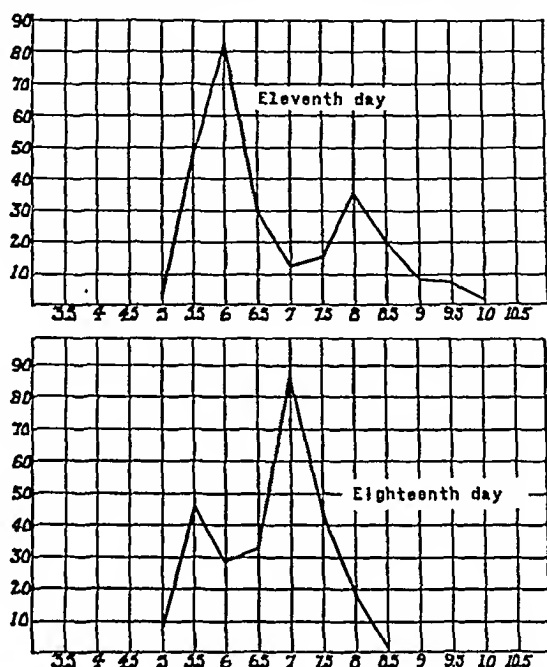


CHART 5.—Bi-modal Price-Jones curves showing the slightly macrocytic response after injection of hemolysin and the progressive decrease in the diameter of both components. The cell diameter prior to injection was 7.12 microns. Note that cells of decreased diameter persist even when the right component is normal in size.

Examination of the stained blood film and of wet preparations gave the impression that the small cells were definitely thicker than normal. Correlation of the diameter and the mean corpuscular volume indicated that the mean corpuscular thickness was definitely increased over the normal figure. The table below contains examples of the figures obtained on the second day.

TABLE 1.—CHANGES IN SIZE AND SHAPE OF ERYTHROCYTES DURING HEMOLYSIS.

Animal No.		Mean corp. vol. (cu. microns).	Diameter (microns).	Thickness (microns).
2	Normal . . . . .	77.7	7.12	2.0
	Second day . . . . .	77.8	6.4	2.35
4	Normal . . . . .	69.5	7.3	1.65
	Second day . . . . .	71.8	5.7	2.8
7	Normal . . . . .	65.9	7.1	1.7
	Second day . . . . .	71.0	5.5	3.0

As the blood smears were followed the large cells which form the second component were observed to exhibit either definite polychromatophilia or reticulation, or to belong to the nucleated group.



On the fifth or sixth day after very large doses of hemolysin, a rare microcyte may be seen which contains only one or two strands of poorly staining reticulum. With this exception, the young cells were not observed to show the diminutions in diameter that was present in the mature forms.

*Fragility.* The change in the fragility of the red cells following the injection of the hemolysin seemed to be roughly proportional to the diminution in diameter and to the corresponding change in the cell thickness. In some instances the cells were so fragile, or hemolysis was proceeding at such a rapid rate, that it was not possible to obtain a hemoglobin-free supernatant fluid even after multiple washings with normal saline. This was particularly true in the acute severe anemias, and in 1 instance all of the cells were hemolyzed in 0.8% saline.

An increased fragility was present as long as the component of cells with small diameters could be demonstrated. However, with the appearance of the larger cells the level of complete hemolysis returned to normal levels, giving a lengthened range of hemolysis. Occasionally, at this stage, hemolysis was not complete until 0.28% or 0.26% saline was reached.

*Comment.* The production of anemia by the injection of hemolytic serum is an old procedure. For a survey of previous observations, reference should be made to the report of Dameshek and Schwartz.<sup>4</sup>

The present findings essentially confirm those previously reported. In normal animals the decrease in diameter of the individual circulating erythrocytes was associated with little or no change in cell volume. This can only be interpreted as meaning that the cell is increasing in thickness or is approaching "sphericity" with the associated increase in fragility. This type of change toward "sphericity" is in sharp contrast with the definite increase in cell volume (associated with slight change in diameter) observed in hypotonic hemolysis by Haden<sup>8</sup> and by Castle and Daland.<sup>2</sup> Stewart<sup>14</sup> observed in 1899 that in hemolysis under the influence of serums, there was no marked increase in the electrical conductivity, but hemolysis by water caused an increase of conductivity, offering evidence that the mechanism of hemolysis is different with different agents.

After 3 to 6 days a definite increase in the mean cell volume is evident. This is associated with an increasing reticulocyte count or an inpouring of even younger cells into the blood stream and compares with the increase in the number of cells with normal or increased diameters observed in the Price Jones curves of these respective days.

Price-Jones curves with widely separated and distinct modes are rarely reported in the literature. Although the transfused red cells in patients with severe pernicious anemia may be recognized by

their normal contour, as contrasted with the bizarre cells present in this condition,<sup>1</sup> they do not cause a bi-modal curve because of the large standard deviation present. A study of the same type in a familial hemolytic anemia with an average cell diameter of 6.6 microns showed a definitely bi-modal curve following transfusion.

Bi-modal curves having shallow depression are presented by Momigliano-Levy and Bairati<sup>10</sup> in cases of familial hemolytic anemia following splenectomy. Also, Dameshek and Schwartz<sup>4</sup> illustrate a bi-modal curve with small macrocytic component during the recovery phase of experimental anemia in guinea-pigs, stating that later the curve may show a more definite macrocytic tendency.

Price-Jones<sup>12b</sup> and Mogensen<sup>9</sup> discuss the possibility of bi-modal curves occurring, and the latter author presents a method for the decomposition of atypical curves into their component parts. This method is somewhat complicated and unnecessary for the curves here presented.

Examination of curves obtained in this series shows that those cells altered in diameter do not all undergo immediate hemolysis. These altered cells remain in the blood stream for varying periods, dependent upon the amount of hemolysin administered. Following small amounts of hemolytic serum, with less change in diameter, they may persist in detectable numbers for approximately 1 month. This particular phenomena suggests an explanation for the failure to demonstrate hemolysin in the serum of many human hemolytic anemias, since, in some instances, mature erythrocytes of normal dimensions may be present in the blood stream with these spherical cells. Serologic investigations, to be reported at a later date, suggest that (with certain exceptions) demonstration of the hemolysin in the serum, even in experimental animals, may be difficult or impossible with the present methods. If correlation with *in vitro* activity of hemolysin is expected, demonstration of circulating hemolysin would rarely be possible unless some factor prevented its combination with erythrocytes.

These small cells, admittedly altered in certain of their characteristics, sufficient to permit identification, persist in the blood stream for a period fully as long as that previously reported for duration of life of the mature erythrocyte of this animal. Eaton and Damren<sup>5</sup> give 16 days based on periods of regeneration while Escobar and Baldwin<sup>6</sup> place the duration at 16 to 23 days, using the response to change in oxygen pressure.

The other component of the curves may be composed either of cells of nearly normal diameters or of cells of increased diameter. A macrocytic response was obtained in this same type of experimental anemia by Dameshek and Schwartz<sup>4</sup> and by Muir and McNee.<sup>11</sup> Price-Jones<sup>12a</sup> shows a similar response after phenylhydrazine poisoning in rabbits, but the data do not permit the plotting of curves.

The course of these curves suggests maturation of these cells in the blood stream, in that as recovery from the anemia progresses the average diameter tends to return gradually toward normal. This return is associated with a diminution in the reticulocyte count suggesting that the demand on the bone marrow is lessened and is associated with a normal or lowered pigment excretion.

When the two components of the curves are almost fused, rather than being widely separated, the picture closely simulates certain phases of human hemolytic anemias, particularly "atypical" cases.

The findings presented suggest an explanation for the cell destruction, "spherocytosis," increased fragility, and certain other phases of human hemolytic anemias. They do not afford an explanation for some features seen in certain of these cases. It is possible that these changes may be obtained with multiple injections of hemolysin on cells previously altered in size and shape. Further work is now in progress along these lines.

**Conclusion.** 1. The administration of a specific hemolysin to the donor animal (dog) is followed by a fall in the erythrocyte and hemoglobin levels, proportional to the amount of hemolysin administered and to the titer of the hemolysin.

2. In the process of cell destruction due to hemolysin (in contrast to the mechanism of hypotonic hemolysis) the erythrocytes approach a spherical form by a diminution in diameter associated with little or no increase in corpuscular volume.

3. This approach to sphericity is paralleled by proportionately decreased resistance to hypotonic hemolysis.

4. The length of life in the blood stream of the erythrocytes altered by the hemolysin is inversely proportional to the amount and titer of the hemolysin administered, and survival periods up to 1 month have been observed.

5. Factors pointing toward maturation of the cells entering the blood stream as response to the anemia are discussed.

The authors wish to express their appreciation for the helpful suggestions and criticism offered by Drs. J. M. Hill, G. T. Caldwell, and H. M. Winans, and to Mr. Lewis Waters for preparation of the graphs.

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# THE EFFECTS OF SULFANILAMIDE AND SULFAPYRIDINE UPON THE BLOOD PIGMENTS OF WHITE RATS.

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In a recent paper in this journal Machella and Higgins<sup>3</sup> report that the daily administration to white rats of sulfanilamide, 1000 mg. per kg., produced a marked cyanosis; whereas Wendel<sup>7</sup> states that in his experience sulfanilamide did not produce methemoglobin in rats or in dogs, rabbits and mice. It was then of interest to determine whether the cyanosis observed in rats was due to some derivative of sulfanilamide as has been suggested<sup>5</sup> or to some other altered hemoglobin such as sulfhemoglobin. Machella and Higgins<sup>3</sup> found that the cyanosis from neoprontosil and sulfapyridine at the same dose level was less pronounced.

In the present study we have determined the concentrations of methemoglobin, sulfhemoglobin and total hemoglobin in the blood of rats that receive daily doses of sulfanilamide\* or of sulfapyridine.\*

**Procedure.** Adult white rats were for 30 days given daily doses by mouth of a 2% acacia suspension of the drug. The concentration of the drug was so adjusted that they received 10 cc. of the suspension per kg. body weight. The daily dose of sulfanilamide was 700 mg. per kg. or approximately one-tenth the 50% fatal dose as determined by Molitor and Robinson.<sup>4</sup> Since the sulfanilamide portion of the sulfapyridine molecule is probably the part associated with methemoglobin formation it was decided that, for purposes of comparison, approximately equi-molecular doses of the two should be given. The dose of sulfapyridine was, accordingly, 1050 mg. per kg.

Methemoglobin, sulfhemoglobin and total hemoglobin were determined at the end of the 30-day period by the method of Evelyn and Malloy,<sup>2</sup> using the Evelyn photoelectric colorimeter. By this method each of the pigments is probably determined with an error of less than 0.2 gm. per 100 cc. Blood was obtained by clipping the tail.

**Results.** The results are summarized in Table 1.

Control.			TABLE 1. Sulfanilamide.			Sulfapyridine.		
M.	S.	T.	M.	S.	T.	M.	S.	T.
0.2	0.2	13.1	0.5	1.6	13.9	0.2	0.2	14.1
0.2	0.2	14.8	1.0	1.4	13.0	0.4	0.3	14.8
0.4	0.1	14.0	0.6	2.0	13.3	0.4	0.7	14.4
0.3	0.2	14.3	0.6	2.2	13.3	0.7	0.2	15.9
0.2	0.1	13.2	0.5	1.2	13.1	0.7	0.1	15.4
0.2	0.1	13.9	0.5	0.8	12.1	0.7	0.1	13.8
0.2	0.1	14.2	0.8	1.4	13.2	0.7	0.2	12.4
0.2	0.2	16.5	0.8	1.3	13.6	0.7	0.2	13.4
0.3	0.1	16.1						
Mean:								
0.2	0.1	14.5	0.7	1.5	13.2	0.6	0.2	14.5

M = Methemoglobin in grams per 100 cc.

S = Sulfhemoglobin in grams per 100 cc.

T = Total hemoglobin in grams per 100 cc.

\* The sulfanilamide was kindly furnished by the Winthrop Chemical Company; the sulfapyridine, by Merck & Co.

The small amounts of methemoglobin and sulfhemoglobin in the blood of the control animals is frequently greater than the error of the method and is in accord with the report of Ammundsen<sup>1</sup> who found small, but significant, amounts of non-oxygen-combining pigments in the blood of normal subjects. The amounts of methemoglobin formed after sulfanilamide and sulfapyridine were similar but not large. Whereas there was almost no sulfhemoglobin in the blood of rats receiving sulfapyridine there was twice as much sulfhemoglobin as methemoglobin in rats receiving sulfanilamide. In no case was the total altered pigment more than 3 gm. per 100 cc. This was correlated with the observation that none of the animals showed a marked cyanosis. Only in the case of sulfanilamide was there a significant reduction in the total hemoglobin. This is in general agreement with the results of Richardson<sup>6</sup> and of Machella and Higgins<sup>3</sup> who found greater blood destruction after sulfanilamide than after sulfapyridine.

**Summary.** 1. In white rats that had received orally for 1 month daily doses of sulfanilamide, 700 mg. per kg., small, but significant, amounts of methemoglobin and somewhat larger amounts of sulfhemoglobin were found. By comparison with a group of control rats there was a decrease in total hemoglobin of about 10%.

2. Under similar conditions a daily dose of sulfapyridine, 1050 mg. per kg. resulted in a similar amount of methemoglobin without an appreciable amount of sulfhemoglobin. There was no significant reduction in total hemoglobin.

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### CORONARY EMBOLISM: A COMPLICATION OF SYPHILITIC AORTITIS.

#### WITH REPORT OF 3 CASES.

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Occlusion of coronary arteries by thrombosis is a relatively common occurrence, but occlusion by an embolus is rare. In reviewing the autopsy records at the Medical College of Virginia, 3 cases were found in over 3000 autopsies. These cases are of

special interest because the occlusion in each case is the indirect result of syphilitic aortitis. The electrocardiographic tracing in the third case is apparently the only one ever to be recorded in a case of coronary occlusion by an embolus.

**Case Reports.** CASE 1.—H. C., a colored male, aged 37, was awakened suddenly at 10 P.M. on Dec. 16, 1936, with a violent pain in his chest and mid-epigastrium; he became nauseated and began to vomit. These symptoms continued and got worse; at 2 A.M. he was brought to the St. Philip Hospital emergency room. His past history revealed that he had had several attacks of "acute indigestion," but other than this there was nothing of significance. He was apparently in good health when he retired on December 16.

Examination revealed a well-developed and -nourished colored male, acutely ill, perspiring freely, thrashing about in bed, vomiting copious amounts of undigested food, coughing, and complaining of severe pain in his chest and mid-epigastrium. His temperature was 96°, neither radial pulse could be felt, and his blood pressure did not register. There was marked distention of his neck veins. The heart sounds could not be heard. The chest was normal to percussion and auscultation. The abdomen was relaxed, no masses were felt, and there was tenderness on pressure in the epigastrium. The extremities were cold and moist.

At 3 A.M. the patient became more restless, his blood pressure still did not register, and his pulse could not be felt. He died at 3.45 A.M.

*Autopsy.* Syphilitic aortitis, mural thrombus in the arch of the aorta, embolus in the orifice of the left coronary artery, acute dilatation of the heart. Pulmonary edema.

*Gross Description* (abstract of protocol). The heart is moderately enlarged and both ventricles are considerably dilated. The epicardium, endocardium and valvular apparatus are intact. The myocardium is slightly relaxed, but not soft, and shows no foci.

Coronary arteries: There is no sclerosis. The left coronary artery is occluded at its mouth by a cylindrical antemortem thrombus.

Aorta: The ascending aorta is normal in caliber and reveals the characteristic findings of syphilitic mesaortitis with slight narrowing of the mouth of the coronary artery. There is grossly little evidence of atherosclerosis. Immediately above the commissure between the left and right aortic cusp there is a mural thrombus firmly attached to the aortic wall.

Lungs: Both lungs are heavy, soggy, and sections show large amounts of clear fluid. There are no other lesions in the lungs.

*Microscopic Description.* Heart: There is no evidence of myocardial degeneration or necrosis.

Aorta: There is marked fibrosis and thickening of the intima with overlying attached thrombotic material composed chiefly of fibrin and platelets. The media reveals severe scarring, metaplasia and marked vascularization. There is dense lymphocytic and plasma cellular infiltration and disintegration of elastic fibers. The inflammatory infiltration about the vasa vasorum in the adventitia is even more extensive and severe than the lesions in the media.

CASE 2.—W. B., a 32-year-old colored male, was in good health until 9.30 A.M., Jan. 7, 1939. While delivering ice he was taken suddenly with a severe pain in his chest which caused him to fall to the floor. He remained conscious and was brought to the St. Philip Hospital emergency room. His past history revealed nothing of significance.

Examination showed a well-developed and -nourished colored male propped up in bed, with short rapid respirations, cold clammy skin, and suffering from severe substernal pain. His temperature was 98.6°; neither radial pulse could be felt; his blood pressure was 65/50. The heart sounds

TABLE 1.—CASES OF CORONARY EMBOLISM.

No.	Author.	Year.	Age.	Sex.	Source.	Branch.	Death.	Condition of C. A.	Condition of myocardium.
1	Virchow	1856	27	F	Endocarditis	Several	?		
2	Huber	1882	64	M	Thrombosis in l. cor.	L. D.	Sudden		
3	Korczynski	1887	38	F	Endocarditis ?	L. D.	Sudden	Marked sclerosis	Fibrous myocarditis
4	Hektoen	1892	32	M	Thrombus on norta	L. M.	Sudden		
5	Rolleston	1896	17	M	Thrombus on left ventricle	L. M.	Sudden	Few ntheromatous plaques	No infarction
6	Oestreich	1896	32	M	Pedunculated thrombus on wall of aorta, closed orifice at right	L. M. and rt. orifice	Sudden	No sclerosis	
7	Chiari	1897	32	M	Thrombus nn norta	L. M.	Sudden		
8	Welch	1899	36	F	Endocarditis	L. M.	Sudden		
9	MneCallum	1905		M	Endocarditis	L. M.	Sudden		
10	Lamb	1913	35	M	Endocarditis	L. M.	Sudden		
11	Gallavardin	1913	63	M	Thrombus of ventricle	L. M.	Gradual		
12	Knufmann	1922	35	M	Thrombus on aorta	L. M.	Sudden		
13	Murray	1926		M	Vegetation on norta	?	Sudden	?	?
14	Wolff-White	1926	31	?	Endocarditis	L. M.	Sudden	?	?
15	Wolff-White	1926	43	F	Pelvic thrombosis	L. D.	Sudden	?	?
16	Wolff-White	1926	46	?	Endocarditis	L. D.	Sudden	?	?
17	Wolff-White	1926	23	?	Endocarditis	L. D.	Sudden	?	?
18	Thompson, Evans	1930	25	M	Teratoma of testis	Both	Sudden	?	?
19	Saphir	1933	35	M	Thrombus, rt. femoral vein	L. D.	Sudden	No sclerosis	No infarction
20	Saphir	1933	70	M	Thrombus in rt. coronary	R. D.	Gradual	Marked sclerosis	Infarction
21	Saphir	1933	70	M	Thrombus on norta	R. M.	Sudden	Marked sclerosis, L. D. cor. art. occluded by old thrombus	Myocardial fibrosis
22	Jacobi, Kandler and Silverman	1934	47	F	Femoral thrombosis	L. D.	Sudden	No sclerosis	?
23	Hoseason	1935	36	M	Thrombus on ulcerated nortic cusp	R. M.	Sudden	?	Healthy
24	Garvin and Work	1939	32	M	Endocarditis	L. D. L. C. R. M.	Gradual	No sclerosis	Infarction
25	Garvin and Work	1939	44	M	Endocarditis	L. D.	Gradual	Few atheromatous plaques	Infarction—left vent.
26	Garvin and Work	1939	26	M	Endocarditis	L. D.	Sudden	Coronaries ?	Diffuse fibrosis—no infarction
27	Work	1939	45	M	Endocarditis	L. D. L. C.	Sudden	No sclerosis	No infarction
28	Porter and Vaughnn	1940	37	M	Syph. aortitis	L. M.	5 hr. 45 min.	No sclerosis	No infarction
29	Porter and Vaughan	1940	32	M	Syph. aortitis	L. M.	1 hr.	Very slight atherosclerosis	No infarction
30	Porter and Vaughan	1940	24	M	Syph aortitis	L. D.	10½ hrs.	No sclerosis	No infarction

## Key to abbreviations:

- L. M. Main branch of left coronary artery (before bifurcation)  
 L. D. Descending branch of left coronary artery  
 L. E. Circumflex branch of left coronary artery  
 R. M. Main branch of right coronary artery (before bifurcation)  
 R. D. Descending branch of right coronary artery

were very distant. There was no arrhythmia, and no murmurs were heard. The abdomen and extremities were not remarkable.

The patient was given  $\frac{1}{3}$  gr. of morphine sulphate,  $7\frac{1}{2}$  gr. of caffeine citrate, and placed in an oxygen tent. Pulmonary edema developed and he died at 10.30 A.M.

*Autopsy.* Syphilitic aortitis with mural thrombi in the aorta, complete embolic occlusion of the left coronary artery, narrowing of the ostium of the right coronary artery, multiple myocardial scars, acute dilatation of the left heart, pulmonary edema.

*Gross Description* (abstract of protocol). Heart: Weight, 390 gm. Thickness of the ventricular walls: right, 0.3 cm.; left, 1.4 cm. The epicardium is smooth and glistening. The left ventricle is dilated, the apex rounded. The endocardium is smooth and glistening, and the valvular apparatus appears essentially normal.

Aorta and coronary artery: Immediately distal to the aortic valve there is a row of flat, elevated, smooth, porcelain-like plaques. The largest of these measures 1.5 cm. in diameter and encroaches upon the orifice of the left coronary artery. Rather firmly attached to it are several friable thrombi, pinkish gray in color, which resemble vegetations. Another plaque has involved the mouth of the right coronary artery and has caused considerable narrowing of its orifice. The inner surface of the beginning portion of the aorta in between the plaques shows marked longitudinal wrinkling and puckering and a discrete area of thinning of the aortic wall. The arch of the aorta shows several early atherosclerotic plaques. The descending portion of the aorta is practically free from arteriosclerosis. An embolism of reddish, friable material has completely blocked the first centimeter of the left coronary artery and protrudes from the orifice into the lumen of the aorta for a distance of 5 mm. The remaining portion of this coronary artery as well as the right coronary artery is entirely normal aside from very slight atherosclerosis.

Lungs: Weight—left, 1150 gm.; right, 1200 gm. The lungs are heavy and soggy, and on section, allow large quantities of clear fluid to escape. There are no other pathologic findings.

*Microscopic Description.* Heart: Numerous sections through the myocardium show many areas of myocardial scarring. There is, however, no evidence of acute necrosis.

Aorta: Sections through various portions of the aorta show markedly elevated atherosclerotic plaques of the intima with softening and calcification. The media reveals extensive destruction of its normal architecture by numerous scars, and foci of densely collected round cells composed of lymphocytes and plasma cells. These foci are irregularly distributed in patchy areas throughout the media and often found about new-formed vessels penetrating the media. There is also extensive perivascular round-cell infiltration in the adventitia. The media shows advanced scarring and disintegration of elastic fibers.

CASE 3.—W. W., a 24-year-old colored male, entered the St. Philip Hospital emergency room at 8.30 P.M., May 12, 1939, complaining of severe pain in the chest. One hour before admission, while sitting in a theater, he was seized with a severe epigastric and precardiac pain, became nauseated, left the theater and fainted. He was brought to the hospital by the city ambulance. He was conscious on arrival, he had no symptoms other than those mentioned, no similar previous attacks, and he had been in good health until the onset of his present illness.

Examination revealed a well-developed and nourished colored male, acutely ill, perspiring freely, very restless and suffering from severe pain in the chest. His temperature was  $99^{\circ}$ , pulse rate was 60 and extremely feeble, respiratory rate was 24, and his systolic blood pressure was 62 (diastolic unobtainable) in both arms. Head, eyes, nose, mouth, throat and glands were not remarkable. The neck veins were moderately dis-



tended. The chest was normal to percussion and auscultation. The heart sounds were distant and weak, no murmurs were heard, the rhythm was regular, the apex rate was 60. The apex impulse was neither seen nor felt. The abdomen was soft, but there was no tenderness, and no masses were felt. The extremities were not remarkable.

The patient was examined with the fluoroscope and a feebly pulsating heart observed. The pulsations of the left ventricle were extremely weak. The heart was aortic in type and slightly enlarged.

An electrocardiogram was taken and this showed an absence of the *P* wave in all four leads; an elevated *RT* segment in Leads 1 and 4; a depressed *ST* segment in Leads 2 and 3; and a deep *Q* wave in Lead 4. (Chart 1.) The ventricular rate was 75, and regular. This tracing suggests a nodal rhythm, damage to the intraventricular conduction system, and acute coronary occlusion.

The white blood count was 8850. The differential count was 71% polys, 25% lymphs and 4% monocytes. The patient was given  $\frac{1}{4}$  gr. morphine sulphate at 9 P.M. and 10.30 P.M. and he received very little relief from either injection. At 1 A.M. he became dyspneic and cyanotic, his pulse was 76, irregular and weak; his blood pressure was 90/70. He was placed in an oxygen tent at 8 liters  $O_2$  per minute. Morphine,  $\frac{1}{4}$  gr. was given at 2.30 A.M. and 6.30 A.M.; at 7 o'clock he developed pulmonary edema and died a few minutes later.

*Autopsy.* Syphilitic aortitis with mural thrombus on the aortic wall, embolic occlusion of the left coronary artery at its orifice, acute dilatation of the left heart, pulmonary edema.

*Gross Description* (abstract of protocol). Thickness of ventricular walls: right, 0.3 cm.; left, 1.4 cm. The epicardium is smooth, moist and glistening. The left ventricle is markedly dilated with rounding of apex. There is, however, no flattening of the papillary muscles to be seen. The myocardium is flabby and mottled on the cut surface, streaked with numerous dark red petechial hemorrhages. The endocardium and valvular apparatus are intact.

*Aorta:* The wall of the aorta is somewhat inelastic. It shows at its beginning a wrinkling of its inner surface which cannot be stretched out. There are elevated pearly gray plaques at the site of all three commissures which are firm in consistency and which separate the cusps from each other. There is, however, no evidence of aortic insufficiency in that pseudo-valves at the tract of outflow are missing, nor is the left ventricle hypertrophied, nor are the papillary muscles flattened as would be expected in chronic dilatation. Other than the described changes the aortic wall shows just a few atherosclerotic plaques in the arch and descending portion. At the commissure between the right and left aortic cusp the roughened surface of one of the above-mentioned plaques is covered with friable thrombotic material which is grayish red in color and adherent to the intima. This thrombus is elongated, measuring approximately 10 by 5 mm. at its base, protruding 1 to 2 mm. into the lumen.

*Coronary arteries:* The main branch of the left coronary artery reveals a compact reddish gray friable plug which is slightly adherent to its wall and which is lodged at its mouth, extending just into the circumflex and descending branch of the left coronary artery. It apparently completely obstructs its lumen. The remaining portions of the coronary arteries are elastic and reveal a smooth intima.

*Lungs:* Weight—left, 700 gm.; right, 800 gm. They show no other pathologic findings than extreme edema. They are soggy, and large quantities of clear fluid ooze from the cut surfaces.

*Microscopic Description.* Heart: Numerous sections through various portions of the myocardium do not reveal definite areas of necrosis. The only histopathologic findings are scattered neutrophils in some areas in the interstitial connective tissue with dilated capillaries engorged with red blood cells.

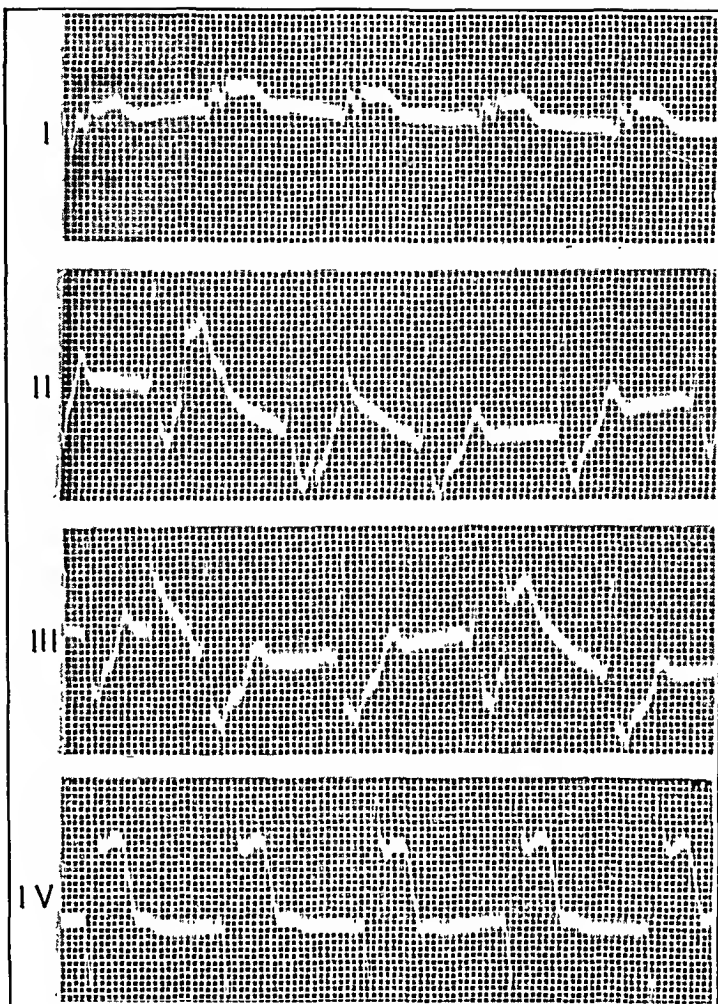


CHART 1.—Case 3. Electrocardiogram.

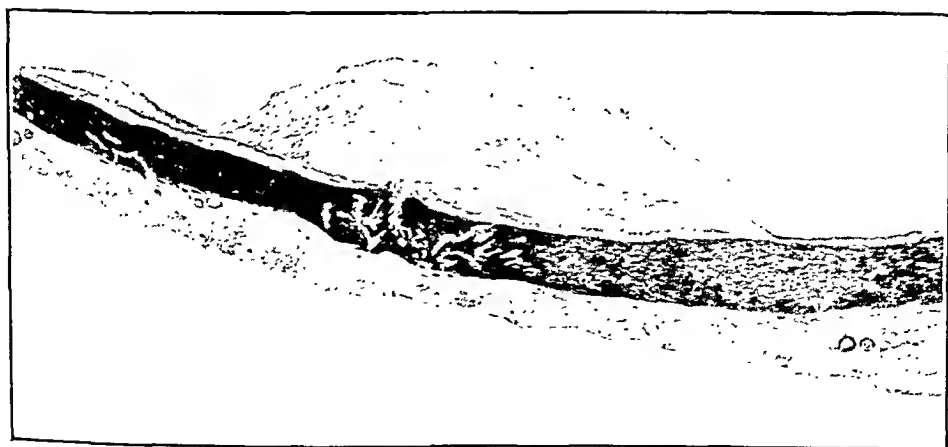


FIG. 1.—Case 3. Aorta showing atheromatous area with overlaying thrombus and syphilitic change in the media.



**Aorta:** Various sections through the beginning portion of the aorta reveal marked metallaxis of the latter with spotted areas of medial degeneration, "moth-eaten" disappearance of elastic fibers, vascularization of the media, marked perivascular round-cell infiltration with lymphocytes and plasma cells in the adventitia and media. One of the sections through the area overlying an atheroma reveals the thrombus to consist of fibrin, platelets and erythrocytes. The thrombus reveals evidence of early organization at its base with capillary budding. It is particularly noticeable that the atheromatous plaques of the intima are confined to such areas of the aortic wall in which there is marked destruction of the media by the syphilitic process (Fig. 1).

**Coronary arteries:** The thrombus in the lumen of the coronary artery is of the same type as that in the aorta, shows definite structure of an antemortem clot. The coronary arteries proper do not show histopathologic changes. There is no evidence of atherosclerosis. Organization of the clot has taken place.

**Discussion.** Saphir<sup>7</sup> reviewed the literature on coronary embolism from 1856 to 1933 and reported only 11 satisfactorily proven cases. Thirteen other cases were mentioned but either because of the brevity of the case reports or lack of autopsy findings, he did not believe they were satisfactorily proven. The 11 cases reported by Saphir will not be discussed here, but we wish to add to this list 7 cases, all mentioned by Saphir, because we believe they have been satisfactorily proven. In addition we shall add the 3 cases reported by Saphir and all other cases reported since 1933. For a case of coronary embolism to be satisfactorily proven, it must be proven at autopsy, and the source of the embolus should be clearly demonstrable.

Oestreich,<sup>6</sup> in 1896, cited the case of a 32-year-old male who died suddenly on his wedding night. Autopsy revealed an arteriosclerotic ulcer in the aorta covered by a thrombus; the thrombus occluded the mouth of the right coronary artery, and gave rise to an embolus which occluded the left main coronary artery. Murray,<sup>5</sup> in 1926, briefly mentioned the case of a young coal miner who died suddenly. Vegetations were found on the aorta and one of the coronary arteries was plugged by an embolus. He did not mention which coronary artery was occluded. Wolff and White,<sup>9</sup> in 1926, mentioned very briefly 4 cases of coronary embolism with sudden death. The left coronary artery was occluded in all 4 cases and the source of the embolus in 3 instances was an endocarditis. In the fourth case, the patient had a patent foramen ovale and the source of the embolus was a pelvic thrombosis. In 1930, Thompson and Evans<sup>8</sup> reported a case of sudden death in a 25-year-old male who had malignant teratoma of both testes. The autopsy findings were: a patent foramen ovale, a large polypoid mass of growth projecting from the left ventricle, and growth emboli in both coronary arteries. Saphir,<sup>7</sup> in 1933, described 3 cases, 2 of which died suddenly. In 2 cases, the right coronary artery was occluded; in 1, the left descending coronary. The sources of the emboli in the 3 cases were: femoral thrombosis, thrombus in the wall of the aorta, and a thrombus in the right coronary artery. In 2 of

these cases there was a marked sclerosis of the coronary vessels. Jacobi, Kendler and Silverman,<sup>3</sup> in 1934, described a case of sudden death in a 47-year-old female with femoral thrombosis. At autopsy a patent foramen ovale was found and an embolus was seen in the left descending coronary artery. There was no sclerosis of the coronary vessels. Hoseason,<sup>2</sup> in 1935, mentioned a case of sudden death in a 36-year-old male who became acutely ill with pain in the chest and epigastrium, nausea and vomiting. At autopsy there was ulceration of the aortic cusp with thrombus formation, and the right coronary artery was occluded by an embolus. Medlar,<sup>4</sup> in 1935, cited a case of coronary embolism with infarction of the myocardium. The patient had extensive bilateral pulmonary tuberculosis, and died rather suddenly. At autopsy, a recent infarction was found in the lateral and upper portion of the left ventricle, but on gross examination there was no evidence of thrombosis or embolism. In microscopic examination, in one of the small coronary arteries, caseous material containing tubercle bacilli was found. We do not feel that this case should be included in the list of satisfactorily proven cases because the embolus was not seen on gross examination. Garvin and Work,<sup>1</sup> in 1939, reported 3 cases of coronary embolism, each of which had been ill 1 month or longer with subacute bacterial endocarditis. At autopsy, vegetations were found on the mitral valve in 2 cases and on the aortic valve in 1 case. Emboli were found in the left descending coronary in 2 instances, and in 1 instance in both coronary arteries. In an addendum to the same paper, Work mentioned another case of subacute bacterial endocarditis with vegetations on the aortic valve, and emboli in the left descending and circumflex arteries.

<i>Age:</i>	10-20	1	
	20-30	5	
	30-40	13	
	40-50	5	
	50-60	0	
	60-70	4	
<i>Sex:</i>	?	2	
	Male	22	
	Female	5	
	?	3	
<i>Source:</i>	Endocarditis		12
	Aortic thrombus		7
	Syphilitic aortitis		3
	Ventricular thrombus		2
	Thrombus of coronary artery		2
	Paradoxical embolism		4
<i>Branch:</i>	Left:		
	Main	12	
	Descending	12	
	Circumflex	2	
	Both	4	
	Right:		
	Main	4	
<i>Death:</i>	Descending	1	
	Sudden	23	
	Gradual	6	
	?	1	

An analysis of the 30 cases as to age, sex, source of the emboli, branch of the coronary artery occluded, and the type of death, is given on the preceding page.

**Comment.** The 3 cases reported are especially interesting in that all were cases of relatively sudden death in colored males with syphilitic aortitis. Textbooks of pathology mention only three complications of syphilitic aortitis; namely, narrowing of the orifice of the coronary arteries, aortic regurgitation, and aneurysm of the aorta. To these we add coronary embolism as one of the possible, though rare, complications.

The pathogenesis of the lesion and mechanism of death appears to be identical in all 3 cases. The gross appearance is characteristic of syphilitic aortitis with moderate amount of atherosclerosis in the first portion of the aorta. The gross impression is supported by histologic studies which reveal active mesaortitis with adventitial round-cell infiltration, destruction of elastic tissue in the media and scar formation. These areas of medial destruction are associated with marked atheromatous changes of the intima, in 1 case the latter is obviously confined to an area just over the medial change. Atherosclerosis in all 3 cases resulted in the formation of mural thrombi attached to the atheromatous plaques. Emboli, from the aforementioned thrombi, resulted in sudden death by complete occlusion of the left coronary arteries in the presence of narrowed orifices of the right coronary arteries. In all 3 cases death was due to acute left-sided heart failure manifested by acute dilatation of the latter and severe pulmonary edema. Death occurred before actual regressive changes in the myocardium had become visible.

**Summary.** Thirty cases of coronary embolism are analyzed as to age, sex, source of the embolus, branch of the coronary artery occluded, and the type of death. Three new cases of coronary embolism are reported, all of which occurred in colored males. Syphilitic aortitis was the indirect source of the embolus in each case.

We wish to express our appreciation to Dr. Paul Kimmelstiel for assisting us in the preparation of the pathologic material.

Another case has been observed at the Medical College of Virginia in which mural thrombi in the first portion of the aorta were demonstrated as an incidental finding. Death in this case was due to trauma. Microscopic sections revealed that the mural thrombi were situated over atheromatous plaques overlying focal areas of fulminant syphilitic aortitis. The syphilitic aortitis was not noticed grossly and did not involve the commissures of the aortic cusps.

This footnote is added to emphasize the fact that mural thrombi on the beginning portion of the aorta without aneurysmal dilatation are apparently more common than has been hitherto assumed.

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## DISSECTING ANEURYSM OF THE AORTA WITH EXPERIMENTAL ATHEROSCLEROSIS.

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It is recognized that dissecting aneurysm of the aorta can heal, and that the newly formed aortic channel can function for years. Patients with such a double aorta can remain symptomless with normal capacity for work. Cases with this type of dissecting aneurysm are relatively rare. As early as 1843 Peacock<sup>6</sup> collected 73 cases of "fully formed dissecting aneurysm." In this group only 4 or 5 cases were of the healed type. In 1934, Shennan<sup>10</sup> analyzed the anatomic and clinical features of 300 cases of dissecting aneurysm of the aorta and pulmonary artery, including 17 cases of his own. In this group, 75 instances are thought by Shennan to be the healed or organizing cylindrical type of dissecting aneurysm; but only about one-half or less of these cases can be regarded as truly healed dissecting aneurysm without subsequent acute tear. One may conclude, therefore, that approximately 1 out of 10 cases of total dissection of the aorta are apt to heal.

The cases to be reported here are unusual, not only because the dissecting aneurysm was completely healed and did not contribute to the causation of death, but also because atherosclerosis was present in the new channel in the wall of the dissecting aneurysm. As a result of the presence of extensive atherosclerosis in the original, as well as in the newly formed aortic walls, the Roentgen ray picture in Case 1 revealed a shadow corresponding to a double aorta.

**Case Reports.** CASE 1.—A. C., a 73-year-old white female, was admitted to the Boston City Hospital on January 11, 1938. She was in good health until the day before admission, when she developed weakness in her right arm and leg, and her speech became thick. Her past history had no significance. She had always been an active person.

On physical examination there was slight facial weakness over the right side. The tongue protruded slightly to the right. The functions of the other cranial nerves were normal. The vessels of the fundi showed arteriosclerosis. The head, neck and lungs were apparently normal. The heart was slightly enlarged to the left; sounds were regular and of good quality. A soft-blowing systolic murmur was heard over the apex. The palpable

arteries were thickened. The arterial pressure was 180 mm. Hg. systolic and 100 diastolic on entry, but subsequently it fluctuated around 150 mm. systolic and 90 diastolic. No organs of the abdomen were palpated. Voluntary motions of the right arm and leg were absent. The reflexes were normal, with the exception of an equivocal Babinski on the right.

The general condition of the patient remained unchanged for 7 days, when she developed a slight respiratory infection, with a temperature of 99.2° F. Four weeks after admission she was allowed to sit up. On March 21, she became acutely ill with signs of bronchopneumonia, and died on April 1.

Examination of numerous specimens of urine failed to reveal abnormal findings. The red blood cell count varied from 4.6 to 4.8 millions; the hemoglobin content from 83 to 109%; and the white blood cell count from 6300 to 9500 previous to the pulmonary infection, rising to 11,400 during the course of the pneumonia. The non-protein nitrogen of the blood was 24 to 33 mg. per 100 cc. The Wassermann and Hinton tests were negative. The phenolphthalein excretion through the kidneys was 46% in 1 hour. The specific gravity of the urine varied from 1.007 to 1.015. The spinal fluid pressure was 140 mm. of H<sub>2</sub>O. The total protein content was 32 mg. per 100 cc. The colloidal gold curve was normal. The spinal fluid Wassermann test was negative. The electrocardiogram revealed sino-auricular tachycardia, with left ventricular predominance; *P-R* interval of 0.2 second and *QRS* 0.08 second. *T*<sub>1</sub> was flat, *T*<sub>2</sub>, *T*<sub>3</sub>, *T*<sub>4</sub> upright. On January 18, a Roentgen ray of the chest was interpreted as showing a calcified outline of the aorta extending outside of the left hilus region. The lung fields were clear. On March 17, the findings were the same, but, in addition, there was bilateral shadow indicating bronchopneumonia. Following the postmortem examination, however, the Roentgen ray picture was reinterpreted as clearly indicating a double shadow corresponding to the calcified walls of the original and of the dissecting aneurysm (Figs. 1 and 2).

*Clinical Diagnoses.* Cerebrovascular thrombosis; right hemiparesis; coronary sclerosis, partial heart block; bilateral bronchopneumonia.

*Necropsy.* Necropsy revealed the following pertinent findings. Both pleural cavities contained some non-bloody fluid and adhesions. In the pericardial cavity there were no adhesions. The heart weight was 300 gm. The orifice and the lumens of the markedly sclerosed and calcified coronary arteries were patent throughout. The myocardium was firm.

*Aorta:* Above the aortic valve and just below the arch, there was a large opening, which divided the aorta into two lumens of about the same size. This double lumen descended to the right common iliac artery, where the new lumen communicated, through an opening, into the iliac artery. The new lumen lay anteriorly and slightly to the left. Both lumens stood out, and the surrounding walls were rigid and calcified in parts. The double aorta could be cut with difficulty, because of the calcium deposits. The intima, both of the original and of the dissected new lumen, was covered with numerous atheromatous deposits. Several strands 1 to 2 mm. in diameter bridged the lumen of the dissecting aneurysm (Fig. 3).

*Lungs:* The right lung weighed 850 gm.; the left one was 680 gm. There was evidence of purulent bronchitis, bronchopneumonia and edema. The spleen, pancreas, and liver were essentially normal. The combined weight of the kidneys was 280 gm. with granular surfaces. The cortex was 0.5 to 3 cm. in depth. The red pyramids were somewhat ill-defined. The pelvis and the ureter were normal. The adrenals were normal. The wall of the bladder was thick. The ovaries and the uterus were small.

*Microscopic Examination.* *Aorta:* Portions of both vascular channels revealed that the original intima showed fibrous thickening containing fatty macrophages. Below the intima the portion of the muscularis contained



many elastic fibers. The surface of the new channel was covered in places with endothelium, beneath which there was a moderately thick layer of connective tissue, infiltrated with fatty macrophages. The connective tissue showed areas of calcification. A moderate amount of elastic tissue was also present in this portion.

The lungs revealed areas of necrotic material containing numerous microorganisms and neutrophils. The kidneys contained scattered hyalinized glomeruli. The arterioles showed marked intimal thickening. The rest of the findings were not pertinent.

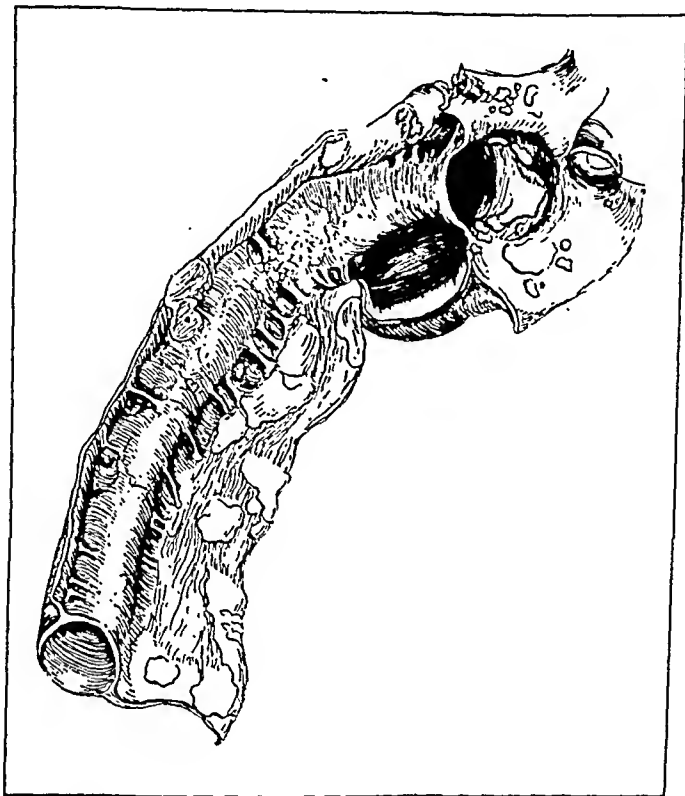


FIG. 3.—Case 1. Gross appearance of the healed atherosclerotic dissecting aneurysm. Atherosclerotic plaques over both the surface of the original aortic wall and the surface of the dissecting aneurysm.

*Anatomic Diagnosis.* Healed dissecting aneurysm of the aorta and right common iliac artery; marked atherosclerosis with calcification of the original and of the dissecting aneurysm; formation of endothelial islands over the dissected aortic surface; coronary sclerosis; bilateral bronchopneumonia with necrosis.

CASE 2.—A 74-year-old white male (Hosp. No. A76816) was admitted to the New Haven Hospital on November 15, 1937, complaining of severe pain in the left flank of 1 week's duration. He had suffered from "high blood pressure and heart trouble" for 10 or 12 years prior to admission. There had been mild dyspnea on exertion for the past 7 years. The onset of the present illness was 14 months before admission when he was seized by sudden severe "crushing" pain in the chest and abdomen, which had spread within 15 minutes to the left leg, shortly to be followed by numbness

and paralysis of the extremity. All these symptoms subsided within 2 hours. However, he suffered from pain in the left loin for 3 weeks. There was slight ankle edema for a few days. He also noticed that his urine was blood-tinged following the severe attack. This pain was associated with profuse sweating but there was never any true cardiac distress. Following this attack he was symptom-free and able to resume his usual mode of living until November 12, 1937, 3 days prior to admission. At this time there was recurrence of severe pain in the left groin which radiated across the abdomen but not along the course of the ureter. There were several vomiting attacks associated with this pain.

When first examined the temperature was 99.4° F., the pulse 98, the respirations 20, the blood pressure in both the right and left arms was 200/100. The patient did not appear seriously ill. The optic fundi showed normal discs and marked sclerosis of the arterioles; the veins were full and there were a few small patches of exudate on the right side. The neck veins were distended. There was dulness at the left interscapular region and a few coarse râles at both lung bases. The heart was percussed as enlarged, 14 cm. in the fifth space. The  $A_2$  was ringing and accentuated. There was a soft systolic blow at the base. Every second heart beat was followed by an extrasystole. The peripheral arteries were sclerosed and the radial and femoral pulsations were equal. No other significant findings were found either on general or neurologic examination.

The essential laboratory data at this time was as follows: Kahn and Wassermann tests of the blood were negative. Hemoglobin was 91%; red blood cells, 5.2 millions; white blood cells, 8500; smear and differential count normal. The urine was smoky in color; specific gravity, 1.020; acid, albumin 1+; sugar, 0; sediment, 6 to 8 red blood cells per high-power field; 1 to 2 white blood cells per high-power field; few cocci. The non-protein nitrogen was 59 mg. Phenolsulphonphthalein excretion, 35% in 2 hours.

The heart, by Roentgen ray examination (Fig. 4) showed increase in its transverse and anteroposterior diameters as a result of left ventricular enlargement. There was considerable widening of the supracardiac shadow of the thoracic aorta with marked dilatation of the aorta seen in the lateral and left anterior oblique projections. The dilatation involved the ascending aorta, the arch and the upper two-thirds of the descending aorta. Roentgen kymography of the heart showed some flattening of the left ventricular waves which showed irregular notching. The waves of the ascending aorta showed an increase in amplitude. Well-defined waves were seen over most of the large descending aorta which projected to the left. The electrocardiogram revealed sino-auricular tachycardia with left-axis deviation.

The pain gradually disappeared after a few days of bed rest. He was discharged on December 4, 1937, with the diagnosis of hypertensive cardiovascular disease; arteriosclerotic aneurysm of the descending aorta, and benign prostatic hypertrophy. One physician suggested the diagnosis of dissecting aneurysm of the aorta.

The patient was subsequently seen in the hospital in March, 1938, with the complaint of shaking chills due to acute pyelonephritis. The physical and Roentgen ray examinations were essentially the same as on the previous admission. The urine showed a heavy growth of *B. coli*.

He was again admitted in May, 1938, with chills and a history of sudden sharp severe pain over the bladder radiating to the back. The findings were essentially the same as before. The blood pressure, left arm, was 160/90; right arm, 150/80; left leg, 200/110; right leg, 130/100 mm. Hg. An electrocardiogram was identical with the previous study except that the

S-T take-off in Leads 2 and 3 were high and definitely higher than in the previous electrocardiogram.

On August 17, 1938, the patient had a sudden pain in the left chest which radiated down to the left hand. On August 19 he had two shaking chills. On August 26, he developed back pain. A maculopapular eruption appeared over the trunk and extremities. He was admitted to the hospital on August 29, 1938.

The temperature was 100.4° F., pulse 98, respirations 24, blood pressure 160/95. There was a loud apical systolic murmur. The remainder of the examination was non-contributory. The white blood cell count was 20,800; neutrophils, 93%. The urine showed a specific gravity of 1.009, albumin 1+, sugar 0, many white blood cells and rod-shaped cocci. The blood and urine cultures were positive for *B. coli*. The non-protein nitrogen was 291 mg. per 100 cc., the CO<sub>2</sub> 24.1 vol. % and the blood chlorides 106. The patient died the day following admission.

*Necropsy.* Overgrowth of prostate; suppurative cystitis, ureteritis and pyelonephritis (bilateral); necrotizing laryngitis, tracheitis and bronchitis; focal pneumonia and pulmonary abscesses (bilateral); generalized arteriosclerosis; dissecting aneurysm of aorta with endothelialization; cardiac hypertrophy; cortical adenoma of right adrenal.

The aorta was increased in circumference throughout its entire length. This increase was least marked near the aortic valve and most marked at the level of the obliterated ductus arteriosus Botalli.

Two and a half centimeters beneath the mouth of the subclavian artery was a transverse fish-mouth opening in the left lateral wall. This mouth communicated with a false passage or aneurysm. This intimal tear was at the level of the obliterated ductus arteriosus but the tear does not involve this structure. The aneurysm had dissected back around the arch of the aorta for a distance of 2.5 cc., stopping just short of the left subclavian artery. The pocket formed by the dissection was filled by an organized thrombus which extended down to within 0.5 cc. of the opening of the aneurysm (Fig. 5).

The descending portion of the aneurysm extended the entire length of the aorta. It was lined throughout by an intact pearly white layer of tissue resembling endothelium. In a few places the endothelium was elevated by small firm, pearly white atherosclerotic plaques. In the thoracic and upper abdominal portions of the aneurysm were several strands not more than 2 mm. in diameter, which bridged the lumen of the aneurysm. These were quite elastic and were covered by smooth white endothelium.

The aneurysm continued down the right common iliac for a distance of 8 cm. when it again ruptured into the true lumen. The right common iliac secured the greater part of its blood supply from the true aorta, as the aneurysmal opening at the bifurcation of the aorta was but a few millimeters in width. This is indicated by the numeral 1 in Figure 5.

The left common iliac received its entire blood supply from the aortic aneurysm. As indicated by the numeral 2 in Figure 5, the aorta had been sealed off and all that remained of the original communication was a small pouch 1.5 cm. in depth in the common iliac artery.

*Microscopic Examination.* Sections of the aorta above the point of rupture showed no lesions. At the upper margin of the aneurysmal opening the endothelium and subendothelial tissues bent backwards upon themselves to form the upper lip. The elastic fibers of the media also described this arc but stopped abruptly just above the margin of the lip. The intima merged imperceptibly into an organizing thrombus. Some of the organization tissue was hyalinized. The thrombus was partially covered by a thin layer of flattened endothelial cells which were continuous with the endothelium of the intima of the lip of the aneurysm. The lower margin was very

similar to that of the upper margin. The only variation was the absence of thrombus.

A section through one of the raised intimal plaques in the wall of the aneurysm showed deposits of hyalinized connective tissue with infiltration by fatty macrophages suggesting early atheromatous changes (Fig. 6).

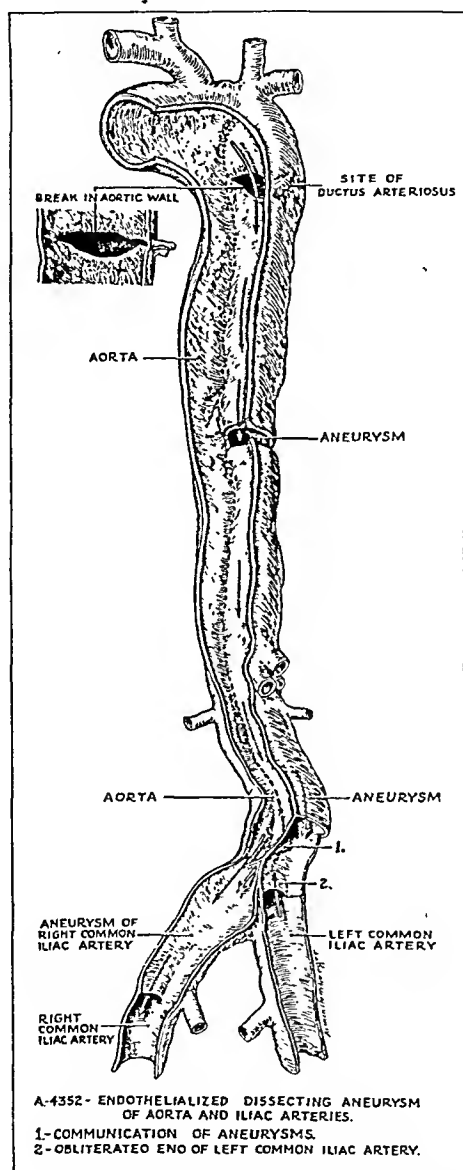


FIG. 5.—Case 2. Gross appearance of the aorta.

All sections of the wall of the aneurysm were covered by intact endothelium. There was a layer of partially hyalinized tissue between the elastic fibers of the media and the endothelium covering the aneurysmal surface. The remnant of the split media in the walls of the aneurysm showed considerable variation in thickness. Neither the adventitia nor the vasa vasorum showed pathologic change.

A cross-section of the right iliac artery showed the aneurysm to be continued into this vessel. The same type of change present in the walls of the aorta was found here. However, there was a well-organized thrombus in the lumen of the iliac artery. This thrombus had been partially recanalized. A portion of the original wall of the iliac artery contained an atheromatous plaque.

The small strands which have been described as spanning the sac of the aneurysm were found on section to be elastic tissue fibers covered by fibrous tissue capped by an endothelial layer. The arrangement of the elastic fibers did not suggest that they represented a portion of a wall of an intercostal vessel. Rather, the arrangement was so irregular as to indicate an origin from a frayed-out strand of elastica from the media of the aorta.

CASE 3.—A 51-year-old male was admitted to the Meriden Hospital in coma on March 25, 1939. The patient was said to have become infected with syphilis in 1918. He was not treated for 8 years and subsequently received sporadic treatment. He had been under the care of a local physician for several months because of hypertension. This ranged in the neighborhood of 260 mm. Hg. systolic and 140 mm. diastolic. The patient was said to have had two rather minor cerebral hemorrhages during the 2 years prior to admission. On the day of admission he was found unconscious in his home. He was immediately brought to the hospital.

The temperature was 97° F., pulse 88, respirations 16, and blood pressure 220/150 mm. Hg. The pupils were contracted and the eyes were deviated to the right. There were moist râles heard throughout both lungs. The heart sounds were regular and of fair quality. There were no murmurs. There was a left-sided hemiplegia.

The spinal fluid revealed 623 red blood cells and 52 white blood cells. The spinal fluid Wassermann was negative. The blood Kline reaction was positive. The non-protein nitrogen was 70 mg. per 100 cc. The hemoglobin was 80%; the red blood cells, 4.3 millions; the white blood cells, 10,000. The urine was alkaline with a specific gravity of 1.018, albumin 0, sugar 0, sediment 0. The patient never regained consciousness while in the hospital and died on March 28, 1939, 3 days following admission.

*Necropsy.* The anatomic findings were massive cerebral hemorrhage in the right frontal lobe involving the corpus striatum and lenticular nuclei and with rupture into the ventricle; focal necrotizing pneumonia with abscess formation (bilateral); benign overgrowth of prostate; dissecting aneurysm of aorta with endothelialization; cardiac hypertrophy; aortical adenoma of adrenal. The heart weighed 510 gm. The wall of the left ventricle measured 15 mm. in thickness while that of the right ventricle measured 4 mm. The heart was otherwise not remarkable.

*Aorta:* Beyond the origin of the left subclavian artery the aorta had been converted into a double tube. Proximal to this point the lining was elevated by irregular, small, opaque patches of dull yellow atheromatous material. At a point just beyond the slight dimpling produced by the ligament of the ductus arteriosus was the mouth of a sac which had a tubular shape and paralleled the course of the aorta proper. At its dorsal margin the opening of the sac was 0.5 cm. beyond the rim of the subclavian artery (Fig. 7). The sac at first lay dorsal to the aorta but approximately at the point 10 cm. above the origin of the celiac axis, it began to be displaced toward the right. It remained to the right and posteriorly for the remainder of its course. The intercostal and upper lumbar vessels took origin chiefly from the new sac by pinpoint orifices but a few originated in the aorta proper from its dorsal surface which was now represented by the inner anterior lining of the false passage. Cord-like, very elastic bands traversed the lumen of the sac and formed a series of ladder-like rungs. The lining

of the sac in contrast to the faintly yellow appearance and relatively smooth surface of the aorta had a gray color and rough, wrinkled contour. As the celiac vessels were approached, the lumen of the aorta became greatly narrowed, and constricted suddenly 2 cm. below the orifice of the superior mesenteric. The iliac vessels were lined by a smooth, light yellow intima resembling that of the aorta proper. This stopped abruptly just above the bifurcation of the vessels forming a slight ridge that demarcated it from the

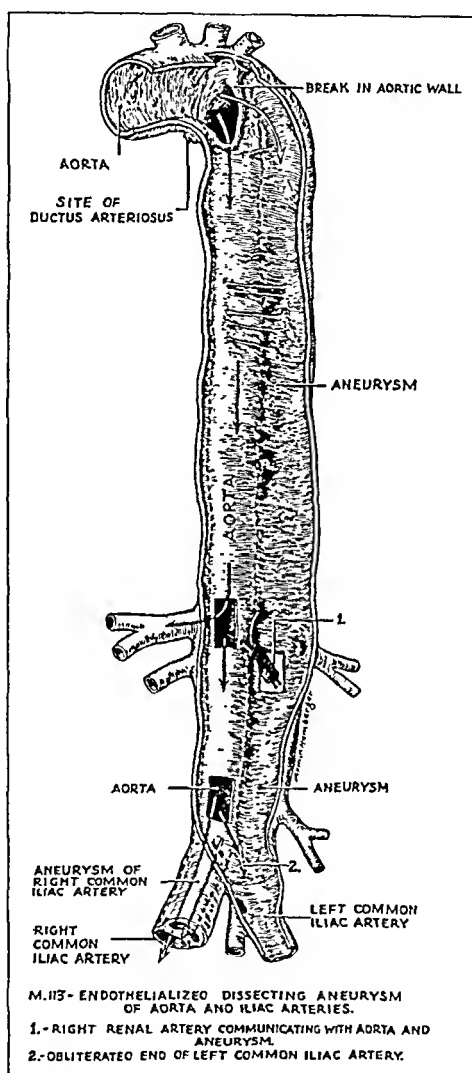


FIG. 7.—Case 3. Gross appearance of the aorta.

rough lining of the false passage. This demarcating ridge was 5 mm. below the linear depression in the medial wall of this sac. The sac had again ruptured into the aorta at this level, namely the bifurcation, but a new wall had formed on the medial side. A probe could be passed into the pinpoint depression, thus demonstrating a communication between the true aorta and the sac at this point. The left internal iliac was a direct continuation of the aorta proper. The external iliac, however, took origin from the

false passage in a linear, almost vertical channel which admitted a probe. The external iliac was lined by several lamellæ of rough, mottled tan and dark red clots, indicating that complete organization had not occurred in the blood clot that covered the rough lining of the sac in this region. Further course of the dissection was not traced beyond a point 2 cm. below the bifurcation of the internal iliac. It is probable, however, that another communication existed between the sac and the true lumen of a branch of the aorta, namely the external iliac, at some lower point that was not observed by the dissection. It is amazing to find that no evidence of bifurcation of a branch of the aorta corresponding to the right common iliac was discovered but that a new wall was established connecting the external iliac with the false sac and completely disestablishing its connection with the original aorta.

*Microscopic Examination.* A section from the aorta above the rupture showed no lesions. At the upper margin of the aneurysmal opening the intima was intact. The elastic fibers of the media were regularly arranged in their usual fashion. There was no scar tissue or cellular infiltration. The media was broken off abruptly at the mouth of the opening. The endothelium was reflected in a sheet over the fibrous tissue which had been laid down over the broken media while the subendothelial tissue fused into the fibrous mass. The lip still covered by intact endothelium joined the external wall of the aneurysm. This wall was made up of fragments of the torn media embedded in fibrous tissue. The adventitia was made up almost entirely of hyalinized fibrous tissue which was piled up to a considerable height. There were many endothelialized vascular channels in the adventitia and media. This was especially prominent in the angle formed by the lip and the aneurysm wall. One of the vasa vasorum in the angle showed proliferation of the subendothelial tissue with marked encroachment upon the lumen. This may have represented a canalized thrombus (Fig. 8).

The walls of the aneurysm were found to be essentially the same as those in Case 2. Also, sections of the strands bridging the aneurysmal sac were almost identical with those in Case 2 (Fig. 9). Changes identical with those in the walls of the aorta and aneurysm were present in the common iliac artery except that there was no endothelium in this part of the sac of the aneurysm. There was a partially organized thrombus attached to the wall of the aneurysm.

*Discussion.* The unusual features of the cases described are: 1, the silent course of healed dissecting aneurysm in Cases 1 and 3; 2, the formation of a functionally competent new aortic channel with newly developed endothelium; 3, the presence of advanced atheromatous lesions in the "intima" and in the deeper layers of the wall of the dissecting aneurysm in 1 case and slight lesions in 2 cases; 4, the Roentgen ray picture of the aorta indicating double channel with partially calcified walls in Case 1; and, 5, normal sized heart in presence of "double aorta" of years' duration in Case 1.

The clinical picture of the onset of dissecting aneurysm was typical in Case 2. It is of interest that within 23 months endothelialization and early atheromatous lesions formed over the surface of the new aortic channel. No history of acute tear was obtained in Cases 1 and 3. The etiology was atherosclerosis in Case 1 and arterial hypertension in Cases 2 and 3. In Case 3 severe arterial hypertension and syphilis coëxisted, but the latter played no rôle

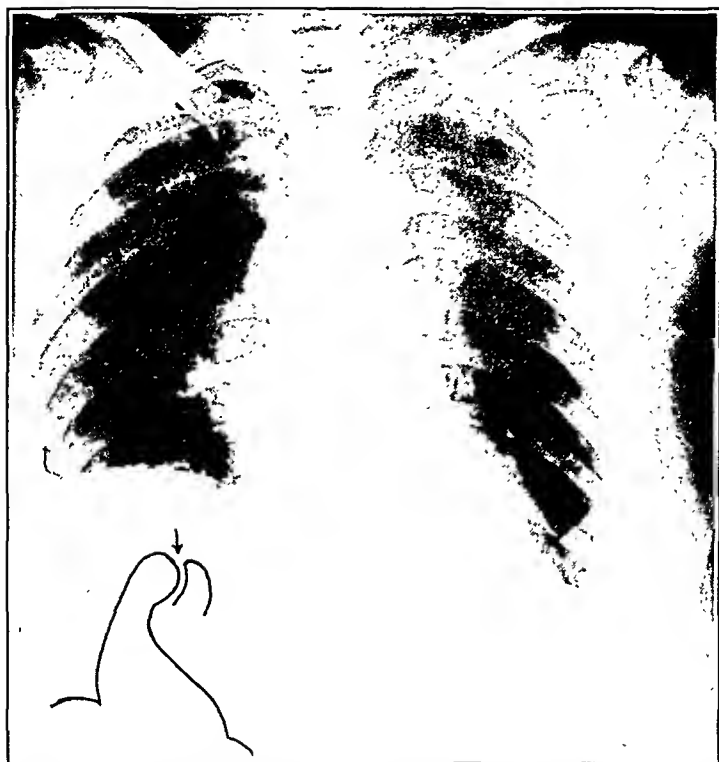


FIG. 1.—Case 1. Roentgen ray picture showing a double shadow corresponding to the calcified walls of the original aorta and of the healed dissecting aneurysm.

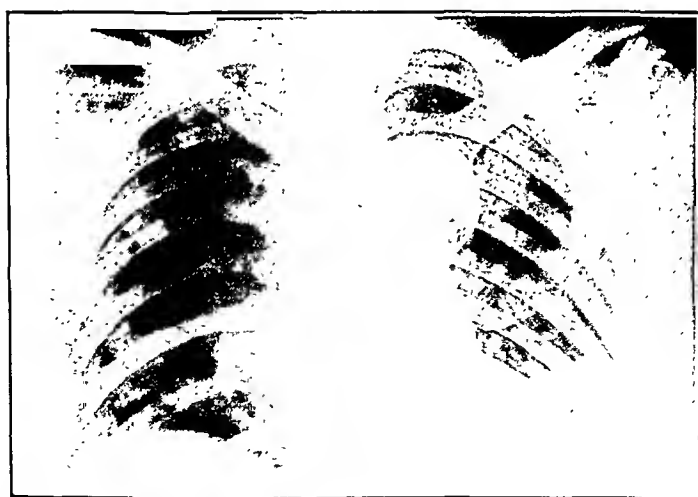


FIG. 2.—Case 1. Roentgen ray picture showing slightly eccentric view of the bulging dissecting aneurysm with a sharp lineal shadow caused by the calcified wall.





FIG. 4.—Case 2. Roentgen ray picture showing a lighter shadow corresponding to the dissecting aneurysm, with a darker center corresponding to the original aorta.

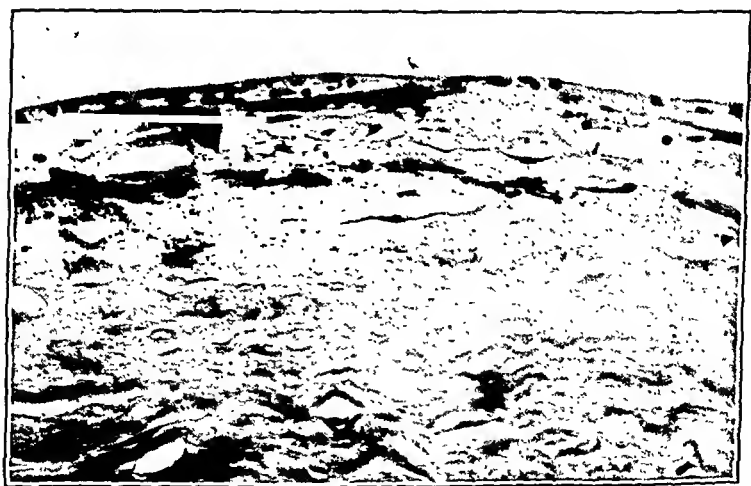


FIG. 6.—Case 2. Early atheromatous change in endothelialized wall of aneurysm. (Hematoxylin and eosin stain,  $\times 225$ .)



FIG. 8.—Case 3. Vasa vasorum showing proliferation of subendothelial tissue with marked encroachment upon the lumen. (Hematoxylin and eosin stain,  $\times 125$ .)

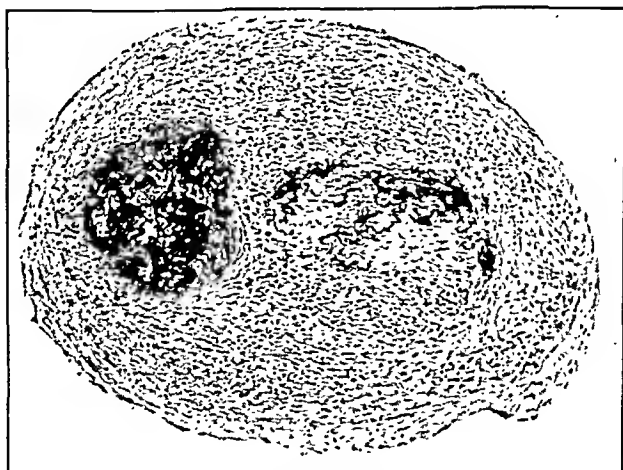


FIG. 9.—Case 3. Cross-section of a strand spanning the aneurysm. (Elastic tissue stain,  $\times 90$ .)



in the formation of the aneurysm. In describing the clinical characteristics of dissecting aneurysm, one of us pointed out that syphilis, as a rule, plays no part in the causation of dissecting aneurysm; and in 1 case, in which syphilitic and dissecting aneurysms coëxisted, the dissection failed to invade the syphilitic aneurysm.<sup>11a,b</sup> Syphilitic inflammation fuses the layers of the aortic wall. Leary and Weiss<sup>4</sup> indicated that in animals as in man atherosclerosis or hypertension is responsible for dissecting aneurysm. They also pointed out that with the apparent increase in the occurrence of dissecting aneurysm and decrease in that of syphilitic aneurysm, the frequency of the two conditions are approaching one another.

Dissecting aneurysm of the aorta may be compatible with good health over many years. As in the cases here reported, in the truly healed dissecting aneurysm, death is caused by other diseases. The majority of cases reported as "healed" dissecting aneurysm, however, are not actually healed cases, because death is caused eventually by secondary tears or vascular accidents related to the aneurysm. Such is the situation in the case recently reported as "healed" by Roberts.<sup>7</sup> In Shennan's series<sup>10</sup> of 79 cases of old "healed" dissecting aneurysm, in 32 instances a final tear or rupture contributed to death; 34 died from heart failure, and the possibility exists that the presence of dissecting aneurysm contributed to the heart failure. There were 6 cases in which, as in Cases 1 and 3, death was caused by cerebral hemorrhage. In Cases 1 and 3, one cannot state whether the onset was silent, or whether the history failed to reveal the acute episode. Cases have been reported<sup>10</sup> in which the onset was known to have occurred years before death.

The formation of new intima with endothelium in dissecting aneurysm has been described in the literature. In 1887, Bostroem<sup>1</sup> reported in detail the case of a 61-year-old male, who died as a result of cerebral hemorrhage, and in whom postmortem examination revealed a healed dissecting aneurysm of the aorta with an endothelial lining of the intima. Bostroem collected other similar cases for the literature. Among others, MacCallum,<sup>5</sup> in 1909, and Williams,<sup>12</sup> in 1920, each reported a case with formation of the endothelium.

The occurrence of atherosclerosis has been commented upon in the literature in a few cases of healed dissecting aneurysm. As early as 1822 Shekelton considered the possibility that a case of healed dissecting aneurysm was an instance of congenital double aorta because the surface of the new intima looked mildly sclerosed. Bouillaud,<sup>2</sup> in 1847, reported the case of a 36-year-old man in whom marked calcareous degeneration was present over the surface of the new lumen. The most instructive case, however, was that reported by Schilling<sup>8</sup> in 1922. The dissection in this 61-year-old man involved the media of the aorta. The new intima, as in

Case 1, is described as irregularly thick with calcareous deposits. Endothelium was also present in the intima of the new aortic channel. In the case of a 38-year-old man reported by Schnurbein,<sup>9</sup> two attacks of unexplained hemoptysis developed years before the terminal heart failure. Mention is made that atherosclerosis was present to a pronounced degree in the upper, and to a mild degree in the lower portion of the dissecting aneurysm.

The question may be raised as to whether, in these cases, a medial atherosclerosis was not present before the dissection. This may be so in part. In Case 1, however, the extensive flat lesions over the intima were identical in every respect with atheromatous lesions observed in usual instances of intimal and medial atherosclerosis of the aorta. One has to assume, therefore, that the dissecting aneurysm was of long duration, and that factors which led to atherosclerosis in the original aortic wall caused similar lesions in the wall of the dissecting aneurysm.

Kienböck and K. Weiss<sup>3</sup> described a case of dissecting aneurysm in which a Roentgen ray picture showed a fusiform dilatation of the descending aorta with a dark central shadow and a lighter peripheral shadow. Such was the picture in Case 2. Wood, Pendergrass and Ostrum<sup>13</sup> described in detail the roentgenographic features of dissecting aneurysm. They found that extending outward from some point in the aortic arch, there may be an arcuate shadow, which may pulsate. Displacement of the esophagus and trachea may occur. At times a shadow caused by the dissecting channel is present along one or more of the large branches of the aortic arch; this is the most pathognomonic roentgenologic sign. Because of the atheromatous changes in the walls of both aortic channels, the Roentgen ray shadow obtained in Case 1 is particularly prominent and unusual in character.

**Summary.** 1. Three cases of healed and functioning dissecting aneurysm are reported. Endothelium and atherosclerosis developed over the internal surface of the new aortic channel. The atherosclerosis of the dissected aortic wall was pronounced in 1 of the cases and mild in 2. In none of the cases did the existence of a double channeled aorta contribute to the death of the patient.

2. In a 73-year-old female, with a healed dissecting aneurysm, the Roentgen ray picture revealed a double shadow corresponding to the double channeled aorta. The surface of the new aortic channel was covered with numerous atherosclerotic plaques and endothelial islands.

3. In Case 2 endothelialization and mild atherosclerosis of the dissecting aneurysm developed within 23 months.

4. The histologic structure of the parallel strands bridging the lumen of the new aortic channel indicate an origin from the frayed-out strands of elastica from the media, rather than intercostal arteries.

5. In approximately 10% of the reported cases dissecting aneurysm heals, is not the cause of death, and can be compatible with adequate functional capacity for years.

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## COMPLETE OCCLUSION OF THE ABDOMINAL AORTA.

## A REVIEW OF SEVEN CASES.

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COMPLETE occlusion of the aorta at its bifurcation has been associated clinically with a well-delineated group of symptoms. The classical syndrome is one of acute onset with severe pain and loss of sensation in the legs, absence of arterial pulsations and rapidly progressive ascending gangrene of the lower extremities with an almost invariable fatal outcome. In a study of the clinical course of 7 patients in whom, at postmortem, complete obstruction of the aorta was found at its bifurcation, we have found that this clinical picture is not a constant one. On the contrary, it appeared in its typical form in only 1 patient. A study of the clinical histories of the others leads us to believe a report of these cases is of interest.

**Review of the Literature.** Welch,<sup>14</sup> in his classic contribution to the subject of thrombosis and embolism in 1899, reviewed 59 cases of complete occlusion of the aorta. In 1921, Hesse<sup>5</sup> contributed an excellent review of 73 cases, including 2 of his own. In 1922, Wylde<sup>16</sup> added 2 more and Banowitch and Ira,<sup>1</sup> in 1928, gave the total number as 110, including 5 of their own cases. In 1935, Rothstein<sup>13</sup> added 1 and stated that there was a total of 123 cases of complete occlusion of the abdominal aorta.

Thrombosis of the abdominal aorta in infants resulting from infection by way of the umbilical cord has been recorded by Moschcowitz,<sup>11</sup> Wheeler,<sup>15</sup> and Rothstein.<sup>13</sup> Bodeff<sup>3</sup> reported a case of a 10-year-old child who developed an occlusion of the abdominal aorta following diphtheria in the absence of intracardiac thrombi. Menasci<sup>10</sup> reported an instance of occlusion of the aorta complicating influenza. Embolism of the abdominal aorta secondary to subacute bacterial endocarditis was noted by Lop<sup>8</sup> and by Langeron.<sup>7</sup>

The larger number of cases has occurred secondary to chronic rheumatic heart disease, usually in patients with mitral stenosis and insufficiency with auricular fibrillation and associated mural thrombi in the left auricle. The number of such cases is high and instances have been reported by Welch,<sup>14</sup> Hesse,<sup>5</sup> Kulenkampff,<sup>6</sup> Wylde,<sup>16</sup> and others. Multiple vascular thromboses involving the abdominal aorta at its bifurcation secondary to a pedunculated thrombus was reported by Fullerton.<sup>4</sup>

**Case Reports.** CASE 1.—A 65-year-old white male, while receiving physiotherapy for varicose veins, developed an ulcer on the outer aspect of the left leg which progressed, and areas of superficial gangrene appeared despite active treatment. On admission, 7 months later, the pertinent physical findings were: heart not enlarged, regular rhythm, blood pressure 180/110; absent popliteal and femoral pulsations; marked pallor on elevation with redness and pain on lowering of legs; several areas of superficial gangrene over dorsum and lateral aspect of left leg. About 6 weeks later, following rapid progression of the gangrene, he developed bronchopneumonia and died.

The essential findings at autopsy were: heart weight, 350 gm.; marked coronary sclerosis with multiple healed myocardial infarcts. There are atheromatous changes in the arch of the aorta which become more marked in the descending portion; 6 cm. below the origin of the superior mesenteric artery, the aorta becomes occluded by old thrombus extending into both common iliac arteries, the external and internal iliac arteries on both sides, and the left femoral artery. A small portion of the lower abdominal aorta also shows a dissecting aneurysm filled with bright red blood clots.

CASE 2.—A 56-year-old white male with intermittent claudication for 15 years, gangrene of the right big toe with healing by conservative treatment two years ago, and recurrence 1½ years later followed by a mid-thigh amputation. Soon afterward, gangrene of the left big toe appeared and quickly progressed upward. The pertinent physical findings on admission were: heart not enlarged, sounds weak, regular rhythm, blood pressure, 200/104; brachial and radial arteries tortuous and hardened; well-healed right mid-thigh stump; left leg cold; an erythematous and puffy area extending one-third the length of the leg; nails of first and second toes absent. A left mid-thigh amputation was performed 2 days after admission, but a cerebral accident occurred 48 hours later and he died in 6 days of bronchopneumonia.

The essential findings at autopsy were: heart weight, 300 gm.; coronary sclerosis and myocardial fibrosis; the aorta shows scattered intimal plaques with ulceration and calcification which increase progressively in the arch and descending portions of the aorta. Just distal to the origin of the renal arteries, an oval mass extends to the bifurcation completely occluding the lumen. This mass is attached to the intima, but is easily stripped, leaving a ragged fibrinous deposit on the intima. The thrombus mass is easily

cut, its periphery is lamellated, the central area is red and contains relatively little fibrous tissue; the thrombus extends into both common iliac arteries.

CASE 3.—A 46-year-old white male developed pain in his lower spine, followed by weakness and inability to walk. Roentgen ray revealed an irregular absorbed area in the third lumbar vertebra which was interpreted as metastatic carcinoma, and was proven by biopsy. The pertinent physical findings were: marked cachexia; heart not enlarged, regular rhythm, blood pressure, 160/100; moderate sclerosis of radial vessels; dorsalis pedis not palpable; marked atrophy of calf muscles with pitting ankle edema. He died in 10 days of inanition.

Autopsy: Carcinoma of pancreas with generalized metastases; heart weight, 300 gm.; marked coronary sclerosis. Aorta is markedly atherosclerotic and inelastic. Its lumen just above the bifurcation is completely occluded by an old gray thrombus which is fixed to the ulcerated intima.

CASE 4.—A 74-year-old white female with known hypertension, auricular fibrillation, and congestive heart failure was suddenly seized with severe pain in both lower extremities and admitted 15 hours later. The essential physical findings were: heart not enlarged, regular rhythm; lower extremities mottled, purple and cold, more marked on the left; no pulsations felt. Patient died the next day following a generalized convulsion.

Autopsy: Heart weight, 280 gm.; marked coronary sclerosis with scattered areas of fibrosis. Aorta shows calcified atherosclerotic plaques in the ascending arch; the lower portion, 3 cm. below the origin of the renal arteries, shows considerable atherosclerosis involving the media and converting it at this level into a rigid tube. This portion and both iliac vessels are filled with red clots adherent to the ulcerated portions of the wall in a few places which can, in general, be removed.

CASE 5.—A 39-year-old housewife with chronic rheumatic cardiovalvular disease for many years and persistent congestive heart failure for 3 years was admitted for numbness of the right foot of 8 days' duration. The essential physical findings were: enlarged heart with systolic and diastolic murmurs at apex, auricular fibrillation, blood pressure, 130/90; enlarged liver; slight pitting edema of lower extremities, dorsalis pedis and popliteal pulsations not felt, hyperesthesia of right foot. She died of a cerebral accident.

Autopsy: Heart weight, 500 gm.; hypertrophy and dilatation of all the chambers with healed rheumatic valvulitis involving aortic, mitral, and tricuspid valves; mural thrombi in both auricles; mild coronary sclerosis. Aorta is elastic, with a few small scattered yellowish plaques. Its lumen at the bifurcation is occluded by a very hard grayish mass which is firmly attached to the wall. This extends to common iliacs, but does not completely occlude their lumens.

CASE 6.—A 38-year-old male with intermittent claudication of 10 years' duration was subjected to a mid-thigh amputation of his left lower extremity for progressive gangrene of 3 months' duration. Seven months later, the toes of his left foot became gangrenous. About 2 years previously the nail of his right index finger was removed for pain, redness and swelling. The essential physical findings were: heart not enlarged, regular rhythm, blood pressure, 160/100; left radial pulse weak, right not elicited; redness and mottling of distal portions of digits of the right hand with thickening of nail-bed; mid-thigh amputation of left lower extremity with well-healed stump; redness and swelling of distal and of dorsum of the left foot with gangrene of first, second and fifth toes. A mid-calf amputation was performed. However, 6 months later, he developed fatal ascending gangrene of the right stump.

Autopsy: Extensive gangrene of left stump and penis, beginning gangrene of right stump; heart weight, 520 gm.; marked hypertrophy and dila-



tation of both ventricles. There is slight coronary sclerosis, healed complete coronary occlusions and an old anterior wall infarct. Aorta is completely occluded by a grayish thrombus which extends from below the renal arteries into the common iliac and right femoral arteries. Microscopically, there is occlusion and recanalization of both right femoral artery and vein.

CASE 7.—A 39-year-old white male, with mild diabetes for 9 years, fatigue and pain in calves in walking for 1 year. During a diathermy treatment, he developed an ulcer on the outer aspect of his right leg which progressed and became gangrenous despite treatment. The pertinent physical findings 9 months later were: heart not enlarged, regular rhythm, blood pressure, 122/83; a discharging punched-out ulcer about the size of a silver dollar on outer middle third of leg.

The ulcer failed to heal; two attempts at skin grafting failed and finally a right supracondylar amputation was performed with satisfactory healing of the stump in 2 months, despite an infection. Three years later, section of the left musculocutaneous nerve was performed for persistent pain in the left big toe. An ulcer formed at the site of incision and broke down repeatedly. Shortly thereafter, he had a sudden seizure of pain in his right forearm with coldness and tingling, loss of radial and brachial pulses, followed by gradual improvement. One year later, he began to experience frequent episodes of precordial pain. Six months before his death, he suffered from an episode of intense pain in the umbilical region which lasted for about a week. Death occurred following a severe anginal seizure.

Autopsy: Well-healed right supracondylar amputation; heart weight, 400 gm.; pericardial adhesions with multiple old coronary occlusion, old healed infarct in posterior wall of left ventricle with a small adherent mural thrombus. Aorta shows mild atherosclerosis; bifurcation is completely occluded by partly organized greenish-red thrombus densely adherent to the ulcerated wall. Both right iliac and femoral arteries are dense fibrous cords; the left iliac and femoral arteries are thickened. There is complete occlusion of the left brachial artery by a recent thrombus.

**Discussion.** This group of 7 cases was obtained from a review of approximately 5350 autopsies performed at this hospital since 1915, an incidence of slightly more than 1 in 1000. Lueth<sup>9</sup> recently also estimated the incidence as 1 case per 1000 hospital admissions. In addition, we encountered numerous cases of partial occlusion of the aorta which are not included in this study.

This series of 7 cases may be divided into three groups: first, a group of 4 (Cases 1 to 4) with atherosclerosis involving for the most part the aorta and coronary arteries; a second group of 2 cases (Cases 6 and 7) with diffuse vascular disease involving the upper extremities in one and the veins in the other; a third type of 1 case (Case 5) with chronic rheumatic cardiovalvular disease with mitral stenosis and insufficiency, auricular fibrillation, and a ball-valve thrombus of the left auricle.

The first group, 3 males and 1 female, ranged in age from 46 to 80. Of these, only 1 (Case 4) presented the classical clinical syndrome of complete occlusion of the aorta on admission. In another of this group (Case 3), there was nothing in the clinical course to suggest involvement of the aorta; but at postmortem the bifurcation was completely occluded by an old gray thrombus. Of interest in the other 2 (Cases 1 and 2) is the rapid progress of gangrene with speedy involvement of the opposite extremity.

In the 2 cases with diffuse vascular disease (Cases 6 and 7), the aortic involvement seems to be a mere incident in the course of a progressive disease involving the entire arterial tree with an arteritis in one and venous involvement in the other. The last case (Case 5) resembles in almost every detail those described in the literature, where complete occlusion at the bifurcation of the aorta occurred as a complication of chronic rheumatic heart disease with arrhythmia and intracardiac thrombi.

Complete occlusion of the aorta may occur by several means: I. Embolism from: A. Thrombus higher in aorta, *i. e.*, aortic aneurysm or thrombosed arteriosclerotic plaque. B. Left side of heart: (1) mural thrombi secondary to myocardial infarct; (2) valvular vegetations—subacute or acute bacterial endocarditis. C. Pulmonary veins—thrombosis. D. Right side of heart—by way of foramen ovale (paradoxical embolism). II. Thrombosis *in situ* associated with: A. Ulcerated atherosclerotic plaque. B. Dissecting aneurysm of aorta. C. Arteritis of abdominal aorta. D. Congenital narrowing of aorta. III. Infection: A. By way of umbilical vessels—in infants. B. Associated with infectious diseases such as diphtheria and influenza.

The differentiation of embolism from thrombosis as a cause of occlusion of the aorta is difficult. Welch<sup>14</sup> pointed out that a decision as to the existence of one or the other is often guess work. As Neuhof<sup>12</sup> pointed out, the mode of onset does not indicate whether one is dealing with embolism or thrombosis, since thrombosis may set in with severe acute symptoms and embolism may produce only intermittent claudication for a long time or no symptoms depending upon the size of the vessel and the collateral circulation.

The generally accepted clinical picture of occlusion at the bifurcation of the aorta is that of a sudden onset with severe acute symptoms and violent pain. Sensory loss, areflexia, numbness, coldness, pallor, cyanosis, and loss of pulsations in the lower extremities develop. Paraplegia and shock rapidly follow with ascending gangrene eventuating rapidly in death. However, most striking in this group of 7 cases is the marked departure from the classical clinical syndrome in 6 cases (Cases 1 to 3, 5 to 7). Indeed, in 1 (Case 3), there was nothing in the clinical history that might be related to the aortic occlusion. One must postulate the presence of an efficient collateral circulation which assumes the responsibility for the vascular integrity of the lower extremities. In such instances as Case 3, the abdominal aorta is physiologically not an "end" artery. According to Bickham,<sup>2</sup> the following collateral areas play an important part in maintaining an adequate blood supply to the lower extremities. There is the internal mammary artery above with the deep epigastric below; the inferior mesenteric above with

the internal pudic below; also, branches of the lumbar arteries above with branches of the internal iliac below.

There are several facts in the clinical course of the other cases which, in retrospect, should have suggested a centrally located occlusive process in the aorta in addition to isolated vascular disease of the extremities. For example, after the onset of gangrene in one big toe in Case 2, progression was so rapid and involvement of the other extremity occurred so early that within 5 months it was found necessary to perform mid-thigh amputation bilaterally. In a second instance (Case 6), 6 months after a successful amputation, rapidly ascending gangrene began at the stump and resulted fatally in a short time. In those cases, we believe the rapid course with early bilateral involvement, recurrence of gangrene at the stump with progression were probably due to the presence of the complete occlusion of the aorta at its bifurcation.

**Summary.** 1. Seven cases of complete occlusion of the aorta at its bifurcation, observed during the course of 5350 autopsies, are presented.

2. Of these, 4 were patients with atherosclerosis of the coronary arteries and aorta, 2 with diffuse vascular disease involving the venous system, and 1 with chronic rheumatic cardiovalvular disease, auricular fibrillation and a ball-valve thrombus of the left auricle.

3. Clinically, the classical picture usually associated with complete occlusion of the aorta at its bifurcation occurred in 1 case. In the remaining 6, the clinical variations were probably due to: 1, differences in the rate of progression of the occlusion; 2, the presence of an adequate collateral circulation; and 3, subsequent development of a more efficient anastomotic circulation.

4. In 2 cases of peripheral arteriosclerosis, a rapid and progressive course with early bilateral involvement and the recurrence and progression of gangrene of the stump should have suggested the existence of an associated occlusive lesion of the aorta.

5. The difficulties inherent in making the differential diagnosis between thrombosis and embolism as the cause of complete occlusion are discussed.

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## THE VALUE OF THE ETHER CIRCULATION TIME IN THE DIAGNOSIS OF RIGHT HEART FAILURE.\*

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SINCE the early work of Blumgart and his associates,<sup>3,4</sup> increasing interest has been manifested in methods for estimating the speed of the circulating blood. Blumgart<sup>2</sup> extensively reviewed the entire subject in 1931, and a bibliography up to 1938 is included in one of the author's papers.<sup>1</sup>

For the past few years we have studied some of the procedures advocated in the measurement of the velocity of blood flow. One method to which we have paid particular attention is the ether arm-to-lung circulation time. As originally described by Hitzig,<sup>8a,b</sup> it consists of the intravenous injection of 5 minims of ether and 3 minims of saline. The end point is the subjective or objective perception of ether in the upper respiratory passages. Since the ether circulation time is an accurate index of the functional activity of the right heart unit, this procedure when done in conjunction with the arm-to-tongue circulation time, permits the differentiation of right and left heart failure.

We propose to give some of our observations obtained in studying the ether circulation time, and consider the value of this procedure in the differential diagnosis of cardiac failure.

**Method.** The test originally suggested by Hitzig<sup>8a,b</sup> and modified by Miller<sup>12</sup> was used. Patients were made to lie in bed until pulse and respiratory rates reached basal levels. After the performance of the calcium gluconate†<sup>1,7</sup> arm-to-tongue time, the needle was left *in situ* and the ether circulation time determined. A mixture of 5 minims of ether and 5 minims of saline is injected into an antecubital vein; the end point is the perception of ether in the upper respiratory passages. Frequently the patient will gasp, cough or grimace in indicating the presence of the ether. In addition, the test is objective as well as subjective, for the observer close to the patient recognizes the odor as promptly as does the patient.

All circulation rates are recorded in seconds and timed by stop-watch from the beginning of the injection to the end point.

**Results.** The velocity of blood flow from arm to lung was determined in 329 patients (see Table 1).

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† Brand of calcium galactogluconogluconate—courteously supplied by Sandoz Chemical Company.

TABLE 1.—SUMMARY OF DATA ON ETHER CIRCULATION TIME.

	Patients.	Deter- minations.	Range (sec.).	Average (sec.).
Normal . . . . .	184	206	3.3-9.4	5.8
Pulmonary Disease . . . . .	26	27	2.5-10.0	6.1
Cardiac disease:				
Without failure . . . . .	38	40	4.0-8.5	5.8
With failure . . . . .	52	58	7.0-19.0	10.2
Hyperthyroidism . . . . .	20	26	3.6-8.0	4.6
Hypothyroidism . . . . .	9	11	4.0-9.0	6.6

The normal ether arm-to-lung time obtained by Hitzig<sup>8a,b</sup> and others<sup>1,10</sup> ranged from 3.5 to 8.0 seconds, with an average of 5.6 seconds. In 184 patients with no known cardiac or pulmonary disease, the ether time ranged from 3.5 to 9.4 seconds with an average of 5.8 seconds. In only 6 of the 184 cases was it prolonged beyond 8 seconds, and in none beyond 9.4.

One of the most important applications of this test is in the differential diagnosis of dyspnea. Ether times were therefore done on 26 patients having definitely proven pulmonary disease. These included cases of bronchitis, broncho- and lobar pneumonia, empyema, lung abscess, tuberculosis, emphysema, bronchiectasis and bronchial asthma. In only 2 of 27 determinations was the ether time prolonged beyond 8 seconds. Both of these prolonged right heart times occurred in elderly men with arteriosclerosis and pulmonary tuberculosis.

The ether time was determined on 90 patients with some form of heart disease. It is in this group that the greatest deviations from normal occur. In the group as a whole, the ether time varied from 4 to 19 seconds with an average of 8.5 seconds. But if we divide these cases into two groups, those with and without signs or symptoms of cardiac failure, more striking figures are obtained. In those patients in whom no evidence of cardiac failure could be obtained, the ether times were normal. But in those exhibiting some clinical basis for a diagnosis of cardiac failure, the average ether arm-to-lung time was 10.2 seconds.

A number of determinations were also done on patients with hypo- or hyperthyroidism. As seen in Table 1, they fall within normal limits.

**Discussion.** Isolated right heart failure is a rarity. As pointed out by White<sup>16</sup> and others, the commonest cause for right ventricular failure is failure of the left side of the heart. A normal ether time naturally does not preclude the existence of left ventricular insufficiency. But in those cases in which right heart failure must be differentiated from mediastinal or pleural tumor, chronic pulmonary disease, nutritional edema or venous obstruction, the ether arm-to-lung time may yield valuable information.

Hitzig<sup>8a</sup> found that cases of pleuropulmonary disease exhibited normal ether times, and Oppenheimer and Hitzig<sup>13</sup> showed that uncomplicated pulmonary insufficiency is usually attended by nor-

mal circulatory measurements. Weiss and Kleinbart<sup>15</sup> and others<sup>6,13</sup> used the ether test to help differentiate cardiac and pulmonary factors in chronic pulmonary disease, and Plotz<sup>14</sup> used circulation time tests in distinguishing asthmatoïd heart failure from bronchial asthma. Hussey<sup>9</sup> found that the ether time was prolonged only in complete heart failure, in isolated right heart failure, and in isolated incipient right heart failure. Certainly our observations have lent confirmatory evidence to these findings.

Recently a number of observers<sup>5,11</sup> have suggested the use of paraldehyde in determining the right heart time, in preference to ether. The procedure and end results are essentially the same.

**Conclusions.** 1. Ether arm-to-lung circulation times were done on 329 patients.

2. The ether time in 184 normal patients ranged from 3.5 to 9.4 seconds, with an average of 5.8 seconds. Only 6 of the 184 patients had times beyond 8 seconds.

3. In 26 patients with proven pulmonary disease, the ether time ranged from 2.5 to 10 seconds. The average was 6.1 seconds, and only 2 of the 26 patients had times beyond 8 seconds.

4. In 90 patients with cardiac disease, the ether time ranged from 4 to 19 seconds. The average in patients without heart failure was 5.8 seconds, in those with heart failure 10.2 seconds.

5. The ether test is of definite value in the diagnosis of right heart failure, and its differentiation from conditions simulating right heart failure.

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## HUMAN STERNAL BONE MARROW IN HYPERTHYROID AND MYXEDEMATOUS STATES.

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ALTHOUGH much has been written regarding changes in the peripheral blood in thyroid dysfunction, the reports of the condition of the bone marrow in these studies are extremely scanty. For this

reason our finding of consistent hyperplasia of sternal marrow in the thyrotoxicosis and hypoplasia in long-standing myxedema is recorded.

Until 1939 the only reported observations found on human marrow in hypothyroidism were limited to postmortem studies of Langhans.<sup>6</sup> Maresch,<sup>11</sup> Dieterle,<sup>3</sup> and Stoccoda,<sup>15</sup> all of whom found the fatty marrow increased at the expense of the red. In hyperthyroidism, Askanazy<sup>1</sup> stated that this condition usually causes no notable changes in the bone marrow. Renzi and Lenzi<sup>13</sup> recorded differential cell studies on sternal marrows from 17 hyperthyroid and 2 myxedematous individuals. A preliminary report of these observations was published, but no quantitative changes in the nucleated cells of the aspirated marrow were mentioned.

Postmortem marrow findings in thyroidectomized rabbits were reported by Esser,<sup>4</sup> Tatum,<sup>16</sup> and Kunde, Green and Burns,<sup>5</sup> and indicate that the marrow is fatty and hypoplastic. Histologic evidence of increased marrow activity in rabbits stimulated by thyroid was found by Kunde, Green and Burns,<sup>5</sup> and Power.<sup>12</sup>

The numerous publications dealing with the peripheral blood in thyroid disturbances are reviewed by Bomford,<sup>2</sup> and he adds some careful observations on anemia in myxedema. In reporting these Bomford states that marrow biopsy was not in use at the time, and he questions the value of the procedure because all indications point to a diminished total amount of marrow that is qualitatively normal in myxedema.

**Methods.** The method used for obtaining and studying these marrows was devised by Schleicher and Sharp<sup>14</sup> and a more recent article by Limarzi<sup>8</sup> describes the apparatus and procedures in detail. To state it briefly: 1 cc. of sternal marrow is aspirated through a dry 16-gauge needle into a dry syringe and placed immediately into a paraffin-lined tube containing heparin as an anticoagulant; the marrow is transferred to a Wintrobe tube; centrifuged 5 minutes at about 2000 r.p.m.; the layers into which the marrow separates (erythrocytes, nucleated cells, plasma, and red and yellow fat) are recorded; the nucleated cell layer is mixed with an equal volume of plasma in a paraffin chamber; and films of this mixture are made, stained with May-Grunwald-Giemsa dyes, and studied microscopically for cell distribution and types.

Studies of the peripheral blood, drawn immediately before the sternal marrow, is made in all cases and this includes erythrocyte, leukocyte, platelet and hemoglobin determinations, mean corpuscular volume, hemoglobin and hemoglobin percentage, sedimentation rate, icteric index, reticulocyte count and differential leukocyte count.

Over 1200 simultaneous studies of the peripheral blood and sternal marrow, like the above, have been done by members of the hematologic section of the College of Medicine of the University of Illinois, and the findings in thrombocytopenic purpura were recently reported by Limarzi and Schleicher.<sup>9</sup>

While the collection and study of these marrows was in progress, a patient with hyperthyroidism was examined more or less by

accident, the blood and bone marrow work having been done because of the discovery of an enlarged spleen. The aspirated sternal marrow, in this case, was found to contain a higher percentage of nucleated cells (myeloid-erythroid layer) than had been found in any conditions, other than the chronic leukemias and relatively severe anemias, excluding certain aplastic types and those due to acute hemorrhage. Stained smears of these cells showed that the increase was in the myeloid series, and peripheral blood work showed that this increase in the marrow was not reflected peripherally by an increased leukocyte count, as is usually the case in chronic myelogenous leukemia. Subsequently, 11 other patients with hyperthyroidism were found to have comparable marrows, and the findings are recorded below.

Shortly following this, the marrow of a patient with untreated spontaneous myxedema was found to contain a low myeloid-erythroid layer, as compared to "normal," and it was decided that all cases of thyroid dysfunction that could be secured would be studied hematologically.

To date, we have collected and studied 19 with thyrotoxicosis and myxedema, from the Research and Educational, and Cook County Hospitals, and 18 "normal" volunteers and preoperative hernia patients. The myeloid hyperplasia of thyrotoxicosis and hypoplasia of hypothyroidism, as compared to the percentage of nucleated cells found in "normal" aspirated marrow, has been consistent enough in this small number of cases to make it seem worth while reporting.

Chart 1 shows the myeloid-erythroid layer in per cent of total bone marrow aspirated from the sternum in 12 cases of hyperthyroidism, as compared with "normal" and hypothyroid averages.

The clinical symptoms and findings of hyperthyroidism were clean-cut in all except Case 9, who had a coëxisting severe diabetes. Case 11 was one of thyrotoxicosis, which followed the ingestion of 5 gr. of thyroid daily for about 3 months. The thyrotoxicosis in the rest of the cases was thought to be due to glandular dysfunction. All had several tests of basal metabolic rates previous to the aspiration of marrow, which varied from +34% to +150%, with the exception of the first which was +15%. The myeloid-erythroid layer in this case is just above the 6.2% normal average. Beyond this, there does not seem to be much correlation between the height of the layer and the metabolic rate, although most of those with high rates were in higher levels. The rates and levels are as follows:

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
B.M.R.(%)	15	45.0	62.0	34	37.0	45.0	37	38	75	65.0	150.0	72
M.E. layer(%)	7	8.4	9.5	10	11.6	12.5	14	14	16	16.8	20.5	22

Chart 2 shows the level of nucleated cells in the aspirated sternal marrow of 7 patients who were clinically hypothyroids, and had



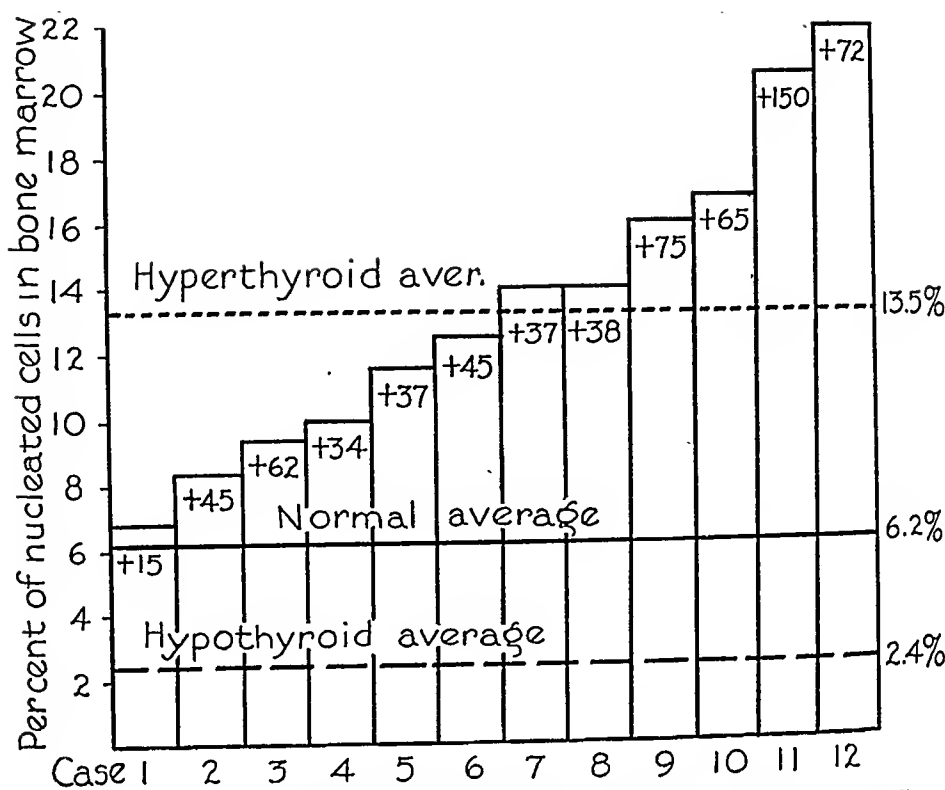


CHART 1.—Per cent of nucleated cells in hyperthyroid bone marrow with metabolic rates.

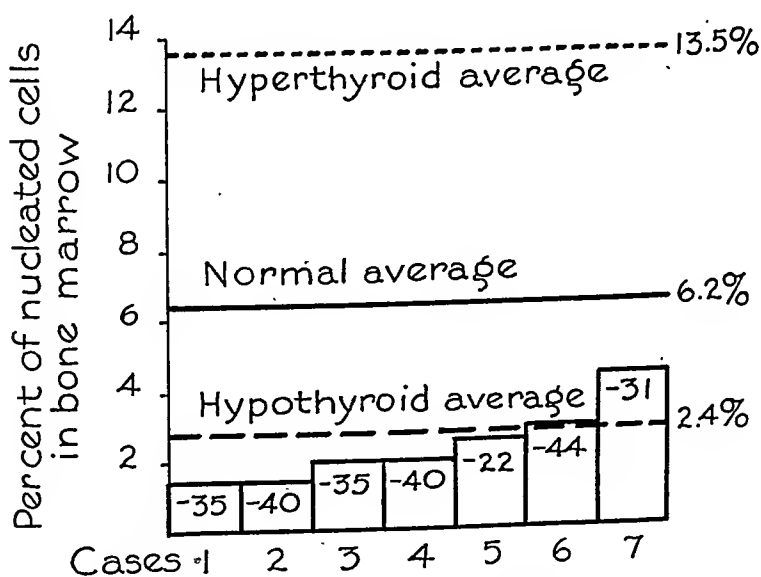


CHART 2.—Per cent of nucleated cells in hypothyroid bone marrows.

repeated low basal metabolic rates. These varied from  $-22\%$  to  $-44\%$ . The patient with the  $-22\%$  rate was a case of post-operative hypothyroidism, all the rest were spontaneous myxedemas. The rates and levels are as follows:

	1.	2.	3.	4.	5.	6.	7.
B.M.R. . . .	$-35.0\%$	$-40.0\%$	$-35\%$	$-40\%$	$-22.7\%$	$-44\%$	$-31.0\%$
M.E. layer . .	1.5%	1.5%	2%	2%	2.5%	3%	4.5%

Chart 3 shows the results obtained from the marrows of 18 "normals." The patients, from whom these marrows were obtained, were chosen because they had no complaints other than the presence of hernia in some, and because studies of the peripheral blood revealed figures that fell within generally accepted normal limits.

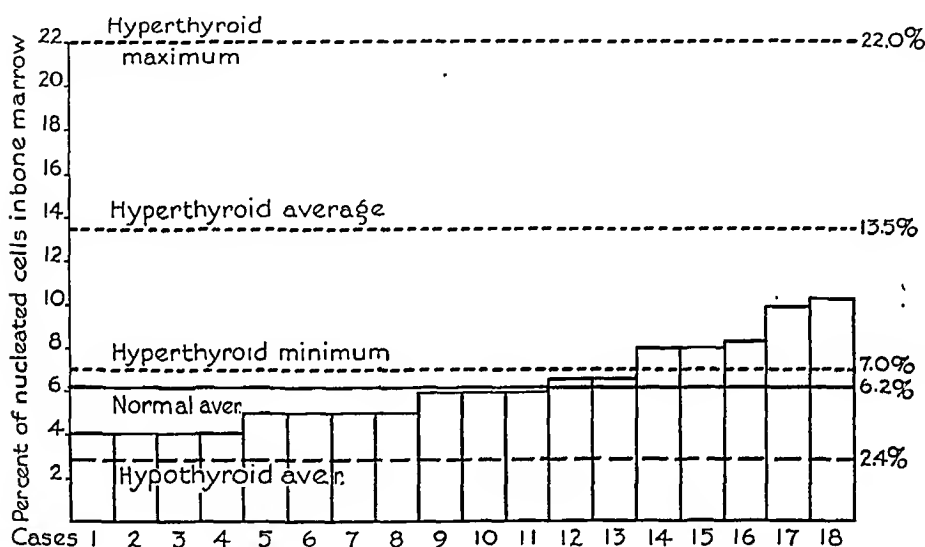


CHART 3.—Per cent of nucleated cells in normal bone marrows.

Peripheral blood studies were done on the patients grouped above as hyperthyroids, "normals," and hypothyroids. The average figures for each of the three groups are tabulated in parallel columns below to facilitate comparison.

From Table 1 it can be seen that in this series the difference between the hyperthyroids and "normals" in peripheral blood findings is not marked. The hyperthyroids show a slight anemia, which depends entirely on a numerical reduction in erythrocytes, there being no significant difference in mean corpuscular volume or hemoglobin concentration between these and the "normals." Differential counts show a slight lymphocytosis in the hyperthyroids, as compared with the "normal" findings, but this is not large.

The hypothyroids show a moderately severe anemia which is, as with the hyperthyroids, due mainly to a reduction in number of the

erythrocytes. The mean corpuscular volume is normal, and the hemoglobin concentration is slightly reduced. The leukocytes quantitatively and qualitatively are practically the same as found for the "normals." One case, the postoperative thyroid (Chart 2, Case 5), showed a moderate macrocytosis (106 cu. microns) which returned to normal (86 cu. microns) after 5 months of thyroid therapy and the return of the marrow to "normal" (Chart 4). This macrocytosis was offset by 1 case (Chart 2, Case 4) in which a microcytosis (67.5 cu. microns) and typical iron-deficiency anemia was found. According to reports of the attending physician, the anemia in this case has cleared up after 4 months of iron and thyroid therapy. The rest of the hypothyroid series showed a reduction in erythrocytes, with no tendency toward macrocytosis or microcytosis.

TABLE 1.—AVERAGE PERIPHERAL BLOOD FIGURES.

	Hyperthyroid.	"Normal."	Hypothyroid.
Hemoglobin, gm./100 cc., Newcomer . . . . .	13.4	14.7	9.4
Erythrocytes, millions/c.mm. . . . .	4.75	5.01	3.51
Leukocytes per c.mm. . . . .	8050	7700	7800
Hematocrit (E) . . . . .	41.2%	45.0%	30.6%
Hematocrit (W.B.C.) . . . . .	Less than 0.5%	Same	Same
Mean corpuscular volume in cubic microns . . . . .	86.7	90.0	88.6
Mean corpuscular hemoglobin in micrograms . . . . .	28.2	29.5	26.8
Mean corpuscular hemoglobin concentration . . . . .	32.5%	32.7%	30.3%
Reticulocytes . . . . .	Less than 1%	Same	Same
Icteric index . . . . .	4 units	6 units	8 units
Neutrophils . . . . .	50.0%	60.4%	55.6%
Eosinophils . . . . .	1.8%	2.8%	2.0%
Basophils . . . . .	0.2%	0.9%	0.8%
Lymphocytes . . . . .	41.6%	28.9%	35.2%
Monocytes . . . . .	6.4%	7.0%	6.4%

Chart 4 shows the change found in the aspirated sternal marrow following therapy with varying amounts of desiccated thyroid and thyroxin in 5 cases of myxedema. The dates of aspiration and basal metabolic rates at the time are shown on the chart. The amount and type of thyroid medication is also shown on the chart, except for the first case, and this will be given in detail below:

**Case Abstract.** The first case of Chart 4 is a male, aged 29, first seen, May 5, 1938, in the hematologic outpatient section of the university clinics. He came directly with a letter from his doctor, stating that he had a peculiar anemia that did not respond to liver or iron, but was, in his doctor's opinion, an atypical pernicious anemia. His complaints at this time were weakness, inability to keep up with things physically or mentally, weight loss, and intolerance to cold. All, except the weight loss, had been gradually increasing for the past year, until 7 weeks previously, when he had become so sluggish that he could no longer keep up with the assembly line, and had been obliged to leave his job of motor-assembler in a farm implements plant. The weight loss had been in the past 8 weeks when he had lost his appetite completely. His wife, who accompanied him, told the examiner confidentially that he had periods of mental confusion lately that frightened her, and that she had signed a complaint, and that unless he improved, the trial for commitment would be held soon. Past and family history were

essentially negative. Physical examination revealed a well-nourished white male 6 feet 2 inches in height, and weighing 175 pounds, who was coöperative, but ponderous and slow in answering questions. He had a dry, thick, pale and cold skin, and a heavy face with infra-orbital puffiness. His pulse was 72, and blood pressure 110/90. He was admitted to the hospital with a diagnosis of spontaneous myxedema, which was borne out by subsequent laboratory findings on May 6, 1938 of B.M.R. —35, blood cholesterol 434 mg. per 100 cc., low voltage E.K.G., and subsequent response to thyroid medication. The metabolic rates and the dates are listed on Chart 4. One grain of desiccated thyroid was given daily from May 17 to 26. Two grains daily were given from May 26 to June 1, then 3 grains daily from June 2 to October 3, at which time the dose was reduced to 1 gr. daily until December 3. Since December 4 he has taken 2 gr. daily. His mental and physical difficulties disappeared rapidly when a dose of 3 gr. daily

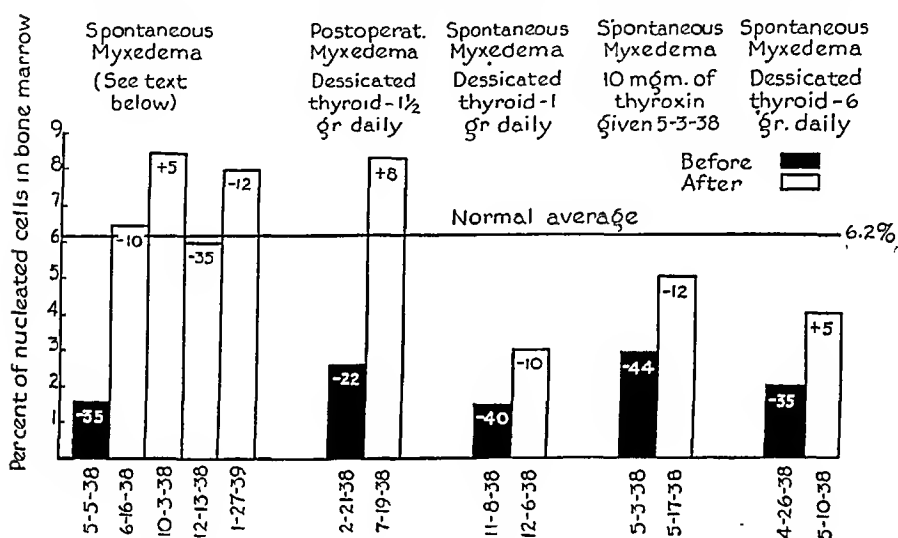


CHART 4.—Effect of thyroid therapy on hypothyroid marrow.

was reached. The response of his metabolic rate and aspirated bone marrow is shown on Chart 4. His blood cholesterol fell to 220 on June 3, 185 on June 8, and 172 on June 21. His peripheral blood findings have changed but little in comparison to the change in his appearance and condition. The first findings (erythrocytes, 4.16 millions; hemoglobin, 12.5 gm. per 100 cc.; mean corp. vol., 89 cu. microns; mean corp. hb. conc., 35%) on May 5, after slight initial fall in red count and hemoglobin, rose gradually until December 13, when they were: erythrocytes, 4.97; hemoglobin, 13.25 gm.; mean corp. vol., 80 cu. microns; mean corp. hb. conc., 33%.

The other treated myxedemas were females, and varied in age from 30 to 54 years. The response of their metabolic rates and the changes found in marrow aspirated from the sternum are also shown on Chart 4.

Chart 5 represents the changes found in sternal marrow and metabolic rates after stopping the ingestion of desiccated thyroid in the first case, and subtotal thyroidectomy done for the relief of thyrotoxicosis in the others. The changes in this group are less

striking than those found in the hypothyroid cases above, and even from the small number studied, one receives the impression that the readjustment downward of the hyperplastic marrow is much slower than the rise of the myxedematous marrows on treatment. The first case in this group is one of thyrotoxicosis that was induced in a 22-year-old female by self-medication for obesity. She had taken 5 gr. of desiccated thyroid daily for about 3 months, and when admitted to the hospital had a B.M.R. of  $+150\%$  (average of several tests after sedation), warm, moist skin, tachycardia, tremor, and was so unstable that she was placed in the Psychopathic Institute for several weeks to prevent her from doing harm to herself. The changes in her peripheral blood were minor compared to those

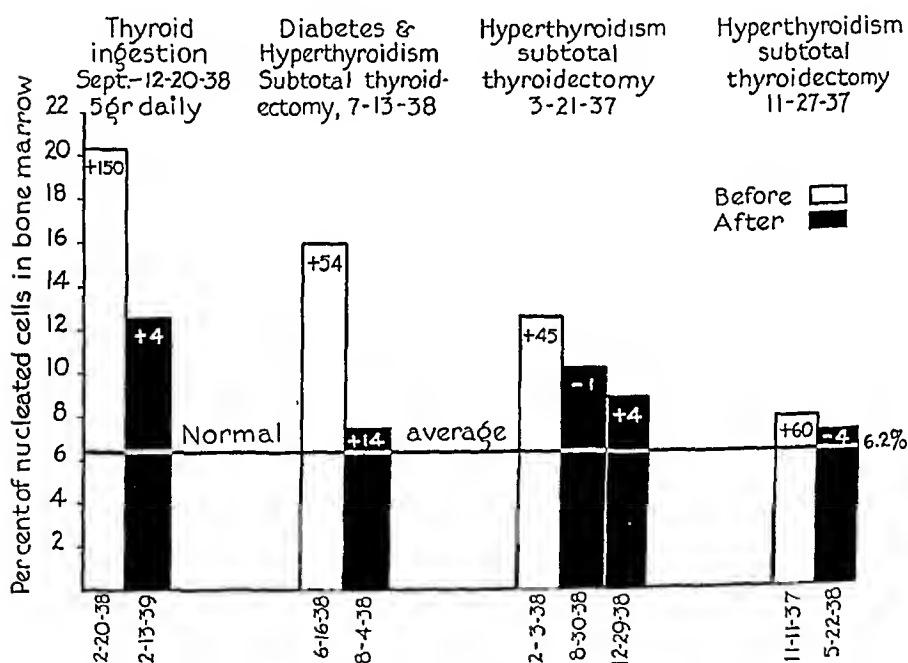


CHART 5.—Reaction of hyperthyroid marrow to withdrawal to thyroid stimulation.

found in the aspirated marrow. In the following list the first figure represents peripheral findings on Dec. 13, 1938, when her B.M.R. was  $+150\%$ , and the second, the findings on Feb. 13, 1939, when her B.M.R. was  $+4\%$ : erythrocytes, 5.68 and 5.39; hemoglobin, 14.25 and 13.8; mean corp. vol., 75 and 82.5; mean corp. hb. conc., 34% and 31%.

In evaluating the results represented by the above charts, it must be remembered that the possibilities for quantitative error are great. The percentage of nucleated cells in the bone marrow shown on the charts is accurate only for the bit of marrow aspirated from the sternum at that time. Dilution with sinusoidal blood must lower the myeloid-erythroid layer occasionally. There have been times

during more than 1200 aspirations that a large sinusoid has obviously been entered, and the aspirated material differs but little from peripheral blood. When this has happened, and such occasions have been surprisingly few, repeated aspiration at a different level of the sternum has been done.

Also it must be remembered that the activity of the sternal marrow, as shown by the percentage of nucleated cells in an aspirated sample, is not a definite indication of the activity in other bones, or of the total mass of active marrow in the body. As has been shown by postmortem examination of the bone marrow of cretins and older individuals, while the sternum, ribs and vertebrae usually contain active red marrow, the marrow of the long bones may be entirely fatty. Bomford,<sup>2</sup> from the scanty evidence available, says that hypoplasia of the active marrow in myxedema is probably on a quantitative basis, that is, that the total active red marrow in the body is reduced in amount, but normal in quality. The findings of this study indicate that the active marrow itself differs from the normal. (See Chart 2.)

Bomford in the same article explains the anemia of myxedema as possibly due to an atrophy of the erythron in adaptation to slowed metabolic processes and diminished oxygen want. The possible reverse of this process in hyperthyroid states is an interesting speculation. Bomford mentions that it seems possible that in polycythemia vera, the increased metabolism is the primary disorder, and the increased erythrocyte formation secondary to this. It was such reasoning that prompted Limarzi, Keeton and Seed<sup>10</sup> to try thyroidectomy in polycythemia vera with some success.

The incidence of polycythemia vera is low when compared with the total incidence of other conditions with increased metabolic rates. Certainly glandular dysfunction without marked blood changes is much more common. Even chronic myelogenous leukemia with a marked rise in the metabolic rate is reported with greater frequency. The bare possibility that the myeloid hyperplasia of the marrow reflected in the peripheral blood in the last-mentioned disease is secondary to the increased metabolism, instead of the cause of it, should not be overlooked. Further speculation might be advanced that a hyperthyroid state is an initiating factor in the development of chronic myelogenous leukemia in susceptible individuals.

The hyperplasia found in the aspirated sternal marrows of 12 individuals with increased metabolic rates (Chart 1) differs markedly from the hyperplasia commonly found in the anemia of iron deficiency, chronic blood loss, hemolytic jaundice and pernicious anemia. Study of stained smears of the nucleated cells shows that the hyperplasia in the anemic cases is due to an increase in the precursors of red cells, normoblasts, and pronormoblasts, while in the hyperthyroid cases, the hyperplasia is myeloid, with an increase in metamyelocytes, myelocytes, promyelocytes, megakaryocytes.

**Summary.** 1. Sternal marrow aspirated from 18 "normal" individuals contained an average of 6.2% nucleated cells.

2. Sternal marrow from 12 individuals with hyperthyroidism contained an average of 13.5% nucleated cells, about  $2\frac{1}{5}$  (217%) times the "normal" finding.

3. Sternal marrow from 7 individuals with hypothyroidism contained an average of 2.4% nucleated cells, a little more than one-third (38%) of the "normal" average.

4. Five cases of hypothyroidism treated with desiccated thyroid or thyroxin, and subsequently studied, showed a marked rise in the percentage of nucleated cells in the sternal marrow.

5. A case of thyrotoxicosis following thyroid ingestion showed a marked decrease in the percentage of nucleated cells in the marrow when the thyroid was stopped. There was a less marked but definite decrease in cases where subtotal thyroidectomy was performed.

6. The hyperplasia found in the marrow of the hyperthyroid individuals was myeloid in character, and was not reflected in the peripheral blood.

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### A QUANTITATIVE STUDY OF THE HEIGHT OF THYROID ACINAR CELLS IN NORMAL AND ABNORMAL THYROIDS.

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A STUDY of the height of thyroid acinar cells and the attempted correlation thereof with any clinical thyroid disease is complicated by the multiplicity of factors known to affect the height of such cells, of which factors disease itself is only one. Indeed, disease is probably an effect of the other factors, at least in part. Presumably one factor that may be operative is the endocrine mediated through the thyrotropic hormone of the anterior pituitary. The potency of this hormonal effect has been more definitely confirmed

in recent years in experimental animals by observations such as those of Grant,<sup>5</sup> noting an increase in size of acinar cells during metamorphosis in amphibia, and those of Rawson and Starr,<sup>9</sup> definitely establishing a quantitative correlation of increased height of thyroid acinar cells with injection of thyrotropic hormone in guinea pigs. Also, it is well known that the heights of these cells tend to increase during menstruation and pregnancy, and as the result of cold. According to Aron and Dobrzaniecki,<sup>3</sup> while the cervical sympathetics exert no effect on cell size of themselves, their presence is necessary for the action of the pituitary. Flattening of the epithelium, together with increased fibrosis, is found in the thyroids of the aged.<sup>6</sup>

These effects on cell height and thyroid activity may be exerted unevenly, so that only a portion of the thyroid is active at one time. It would appear, according to Aron,<sup>2</sup> that some acini are actively secreting all the time but that the majority work in cycles. In pathologic thyroids this diversity of activity is especially evident, and indeed reaches its culmination, in nodular goiters. This cyclic variation in thyroid function and structure, as described by Marine and amplified by Rienhoff<sup>10</sup> helps to explain the wide variation in appearance of different sections, and the great difficulty in identifying a nodular goitre as toxic or non-toxic microscopically.

There have been many means devised to correlate the histologic appearance of sections with pathologic conditions and function. McFarland and Robson<sup>7</sup> found wide variations in acinar diameters in normal glands and no correlation between histologic appearance and age, sex or non-thyroid diseases. The mitotic index of Loeb is an accurate and objective index of thyroid activity, but is an exhausting and time-consuming method.<sup>4</sup> At present, dependence is usually placed on the impressions of the individual observer, a method neither open to objective analysis nor objectively accurate.

The purpose of these investigations was to see if any correlation of cell height and function existed in human thyroids, especially as it might aid in establishing an index whereby nodular goitres could be classified as to activity.

**Method.** The methods used in these experiments are modeled after those used by Rawson and Starr<sup>9</sup> in their experiments on guinea pigs. They correlated the average height and the mode of distribution of heights of 200 acinar cells as a measure of thyroid activity produced by the injection of thyrotropic hormone.

A micrometer scale fitted into the eyepiece of the microscope was used to measure the height of the cells, using an oil immersion objective. With the optical set-up used, and calibrated with a blood counting chamber, one unit is approximately equal to  $1.4 \mu$ . The diameter was measured in all cases at a point crossing the nucleus and on a line along the radius of the acinus. The cells were measured in blocks of 100 from 100 separate acini chosen at random according to where the scale happened to fall as the slide was systematically moved across the stage. The only provisos were that the acini be open and that the cell boundaries be distinguishable.



*Normal Thyroids.* Thyroids were obtained from autopsies at Philadelphia General Hospital. The specimens were chosen at random, but an attempt was made to obtain specimens only from those in whom the cause of death had been comparatively acute and consequently not showing the effects of a long siege of illness. Because of the inadequate number of cases no attempt was made to classify the causes of death or attempt to correlate them with the results obtained. On microscopic section all glands appeared normal. In all, 40 normal thyroids were examined, of which 21 were from males between the ages of 20 and 50 and 19 from females between the ages of 20 and 70 (most between 20 and 50). No attempt was made to correlate our findings with age because the number is wholly inadequate.

First, 5 entire thyroids were obtained from male patients and 6 sections equally spaced obtained from each. Two sets of 100 cells were measured from each section of 2 of the glands and from 4 of the 6 sections of a third, and 1 set of 100 cells was measured from each of the other sections. It was found that nothing was to be gained by measuring more than 100 cells from any one of these sections (see Results).

In the remaining 35 glands, 100 cells from each were measured. Thus a total of 40 normal glands was examined, a number sufficiently large to apply statistical methods and obtain reasonably valid results. Statistics for these observations—mean, standard error, and range for each slide and for the group as a whole—were calculated. The first 21 of these normal glands are from men, the last 19 from women. The two groups were compared statistically to determine whether there was any detectable difference between them.

*Toxic Diffuse Goitres.* In the same fashion as with the normal glands, 100 cells from sections of 25 cases of toxic diffuse goitre were examined. Similar statistics were calculated for this group and analyzed.

*Nodular Goitres.* Sections (through the nodules) of 51 surgical specimens of nodular goitres were examined. The slides of all, toxic and non-toxic, were assembled and measured without knowing the clinical diagnosis so as to make the examinations as objective as possible. Because of the variability of different parts of nodular goitres it was deemed advisable to change the technique of examination somewhat. However, the number of sections from any one case was definitely limited. The procedure adopted was to measure 100 cells from one section as above and calculate the statistics. Then, if more sections were available, 50 cells were measured from each of them and if there was any section where the mean of the 50 cells was significantly different from the figure for the original 100, 100 cells from that section were also measured.

The nodular goitres were divided into two groups of 26 and 25 cases respectively, toxic and non-toxic, according to clinical signs of toxicity and basal metabolic rate. The signs of toxicity were given more weight and whenever present the gland was put in the toxic group. Three glands from cases showing definite elevation of BMR (basal metabolic rate) but no clinical signs of toxicity were not considered in the analysis in order to avoid possible borderline cases.

*Results. Normal Thyroids.* Despite the fact that there is a wide variation in measurements of individual cells, there was no difference greater than 0.2 units between the means of any two groups of 100 cells from any one gland of the 5 analyzed in multiple sections. The figure of 0.2 was obtained in only two instances. Inasmuch as twice the standard error is also 0.2 for these means, that difference does not constitute a significant one. Since the standard error of the mean is a measure of the variability of the

material studied, there is no indication that the normal thyroids studied are anything but uniform throughout as regards these means and there is presumably no error entailed in taking 100 cells from any one section of the gland.

When we consider the measurements of all 40 normal glands, we find that the range of means is well limited—from 3.6 to 4.9 units. The cell heights of 25 normal glands (21 males and 4 females) are plotted in Chart 1. The peaks of these curves, which represent the modes, are not so important as their general contour and position which represent graphically their means and distribution. The average of these means is 4.3 units and has a standard deviation of 0.3 units. The standard deviation referred to is a statistic designed to serve as a measure of variability of the whole group of means.

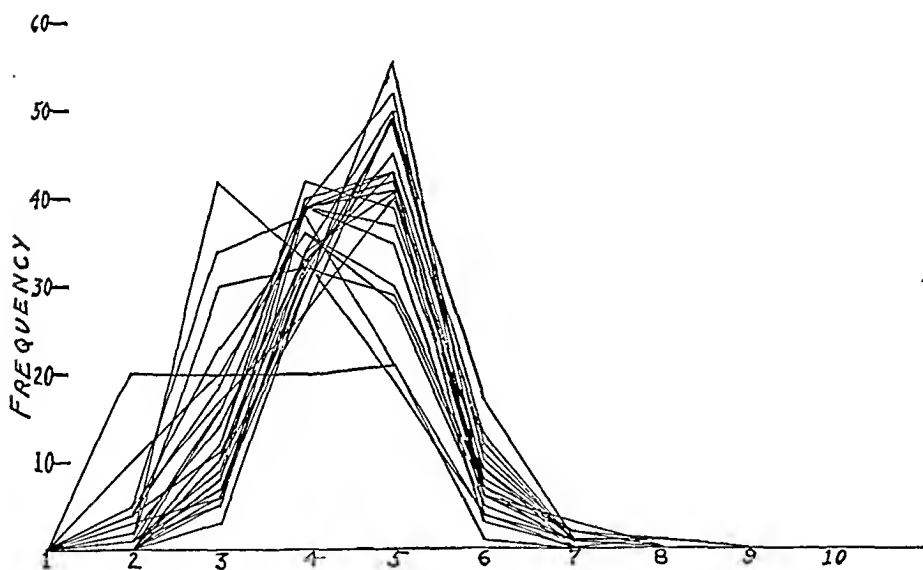


CHART 1.—Normal thyroids. Cell heights in units (1 unit =  $1.4\mu$ .)

So, if the normal glands measured be an adequate and representative sample of normal glands, the indication is that the mean cell height of 100 cells from these or any other normal glands will lie between that average of means plus and minus twice the standard deviation, or between 3.7 and 4.9 units, in over 95% of cases.

When we consider the normal glands in two groups, the first 21 comprising those from males and the remaining 19 from females, we find no statistical difference between the two groups. The average of means for the former is 4.4 units and for the latter is 4.3 units. The difference of 0.1 unit falls far short of statistical significance when we use either the standard error or Student's "t" criterion. (Student's "t" criterion is a measure of variability of means especially designed to be applicable in cases like these where the number

of cases is a little too small for the standard error to be rigidly applicable.)

*Toxic Diffuse Goitres.* Microscopically, sections of toxic diffuse goitres show cells that are obviously larger than those in normal glands. Even after iodine administration the difference is usually still distinguishable. Thus 22 of the 25 glands considered have mean cell heights outside the upper limit established for normal glands, with the average of all 25 means equal to 5.4 units. From the standpoint of variability these glands are intermediate between the normal glands already discussed and the nodular glands to be considered later. Of the 25, 19 have means between 5.0 and 6.0 units, but the others vary considerably. Statistically, the standard deviation of the average of these means is 0.6 units and so the limits

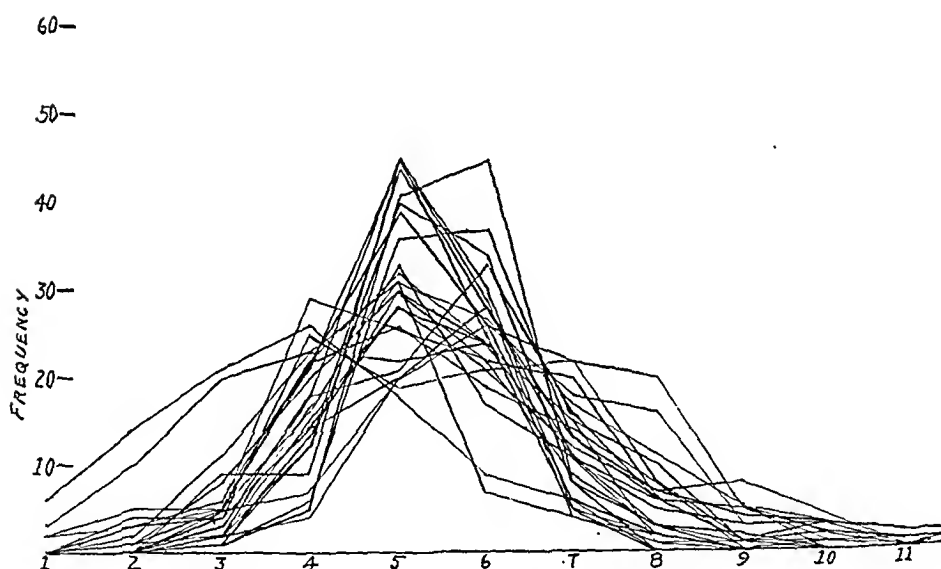


CHART 2.—Toxic diffuse goitres. Cell heights in units (1 unit =  $1.4\mu$ .)

are from 4.2 to 6.6 units for the means of cell heights of toxic diffuse goitres. Such limits are obviously too wide to be of any value. However, there is a very pronounced tendency for such means to be outside the upper limit for normal glands. (See Chart 2.)

*Nodular Goitres.* The variegated microscopic appearance of nodular goitres well described by Marine<sup>8</sup> is amply attested by the wide variation of cell heights and by the occasional variation in the mean heights of cells from different sections of the same gland (see Charts 3 and 4).

There is no sharp differentiation between the two groups of nodular goitres considered. In general, the means of cell heights from the group of toxic goitres are higher, but there is a wide overlapping in individual cases. Thus, mean heights from at least one

section of 18 of the 26 glands in the toxic group are over 5 units, while the same is true for only 11 in the other group. That propor-

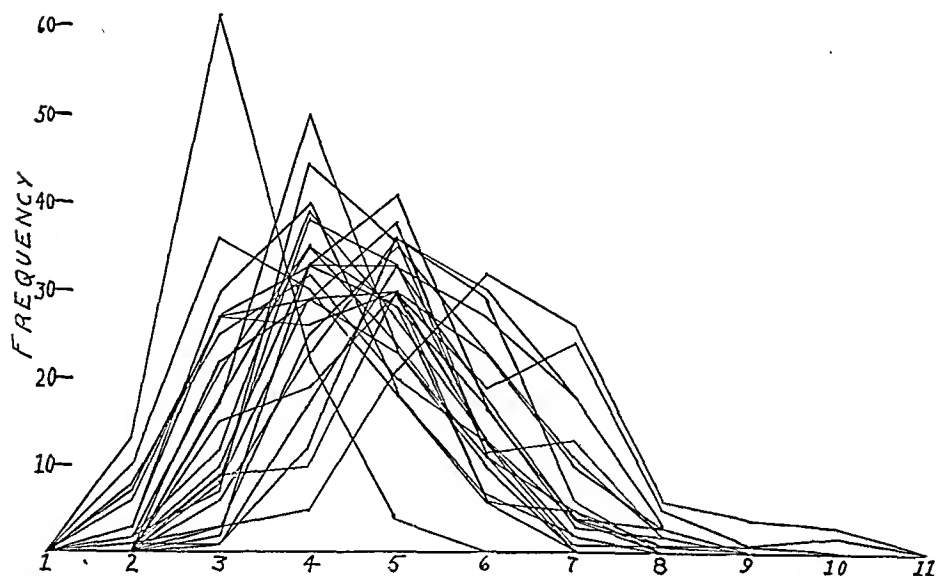


CHART 3.—Nodular goitres—Non-toxic. Cell heights in units (1 unit =  $1.4\mu$ .)

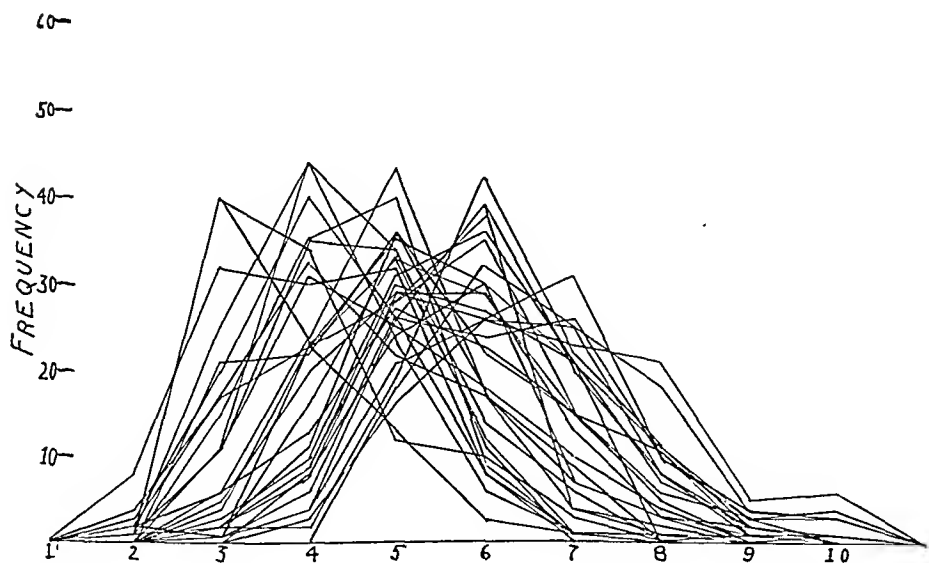


CHART 4.—Nodular goitres—Toxic. Cell heights in units (1 unit =  $1.4\mu$ .)

tion is 69% *versus* 44% outside the upper normal limit. Perhaps this definite tendency would be more apparent in glands where iodine had not been given preoperatively.

Of more value, however, is the fact that 10 of the 26 toxic glands have sections with a mean height of 5.8 units or more—a total of 38.5%. In the non-toxic group there is no mean height greater than 5.7 units. This seems to be a definite difference in the two groups and, although nothing is absolutely proven, it is probable that given a nodular goitre with cells of a mean height of about 6 units or greater, the goitre is toxic. Having an indication of toxicity in even a small percentage of cases is a distinct advantage because the difficulty of recognizing the difference by a subjective examination is such that many pathologists will not attempt the diagnosis. In this regard we were interested to note that of three glands with no associated clinical toxicity but consistently high elevation of

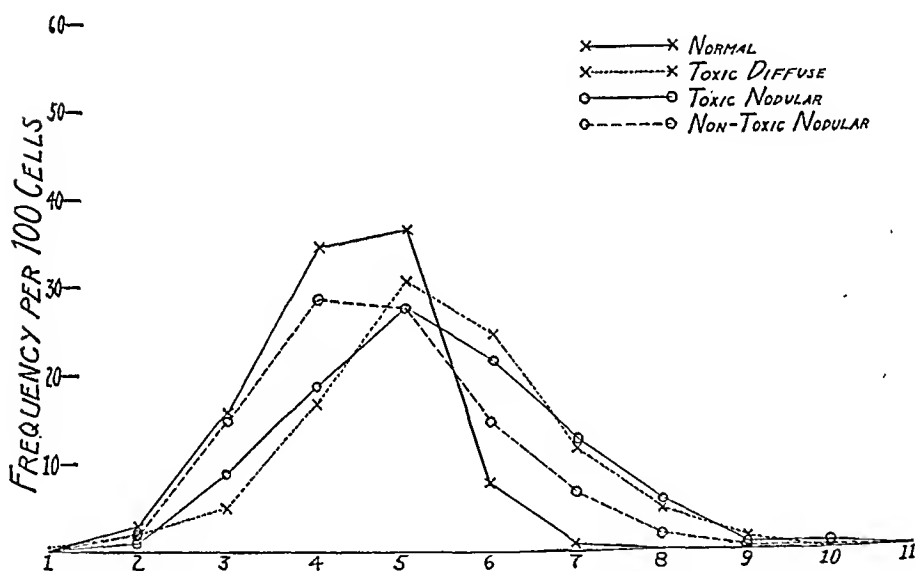


CHART 5.—Normal and pathological thyroids composite curves. Cell heights in units (1 unit =  $1.4 \mu$ )

B.M.R. (not included in the series because of doubt as to classification), two had mean cell heights well above 6 units, which, we would be inclined to believe, indicated at least an impending toxicity manifested now not subjectively but only by increase in B.M.R.

In regard to possible effects of menstrual phase on the pathologic specimens, it is worth noting that goitre operations are preferably performed at a time when the patient is most stable—it is therefore assumed that menstrual effects do not play a rôle.

The problem of studying our human thyroids was complicated by several factors. First, those contributing normal glands were obviously not under the standard conditions of guinea pigs. Second, we have studied thyroids complicated by disease conditions definitely

more complex than a simple excess of hormone, and in all probability involving other factors beside pituitary dysfunction. And third, the disease pictures seen were from pathologic specimens at the University Hospital, where iodine is given routinely preoperatively to cases with toxic goitres and in some cases, when indicated, to those with non-toxic nodular goitres, tending to decrease the height of the glandular cells considerably.

Even under these circumstances, however, differences do appear between our groups of glands and are shown in the composite curves of Chart 5, wherein are plotted the average values of cell heights of each group. The normal curve is high and narrow and to the left of the others showing a comparatively narrow range of heights of relatively low cells. The curve of the toxic diffuse goitres is shifted to the right but is also fairly narrow, indicating greater cell height in a somewhat limited range. The curves of the nodular goitres are broad and low, showing the great variability of cell height, and the generally higher cell height of the toxic goitres is indicated by the shift of that curve to the right.

**Summary and Conclusions.** 1. Single and multiple sections of 116 normal and pathologic thyroid glands were examined microscopically and blocks of 100 acinar cells measured by means of a micrometer scale in the eyepiece. The method is easy, and with practice is comparable to a differential cell count.

2. There was found an almost perfect agreement of means of cell heights in different sections of 5 normal glands.

3. Means from 40 normal glands varied within a narrow range. The range of statistical significance is 3.7 to 4.9 of our units.

4. Twenty-five toxic diffuse goitres were examined and 22 of them had mean cell heights outside the upper limit of normal. The means of these glands were more variable than the normal but there was definite tendency for a fairly close grouping between about 5 and 6 units.

5. Fifty-one nodular goitres were examined and divided into toxic and non-toxic groups.

In general, there was an overlapping of the mean heights of the two groups although those of the former tended to be greater.

Of differential importance, however, was the fact that 38.5% of the former group had mean heights of 5.8 units or greater—a figure higher than any obtained in the latter group.

6. The indication follows that if these results be confirmed, the method used may serve as a useful index for distinguishing toxic nodular goitres, and perhaps for recognizing structural concomitants of thyroid hyperfunction as well.

The author wishes to acknowledge gratefully the help of Dr. I. T. Zeekwer in suggesting the problem, helping obtain material, and offering constructive criticism.

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## INFLUENCE OF ESTROGEN ON THE INSULIN REQUIREMENT OF THE DIABETIC.

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THE first attempt to reduce glycosuria by the use of estrogenic substance was that of Barnes, Regan and Nelson,<sup>1</sup> who reported their results in 1933. Because of the evidence indicating that the administration of the estrogenic hormone may suppress the sex principle of the pituitary, these investigators were interested in determining whether the diabetic principle of the pituitary might likewise be suppressed. Using pancreatectomized dogs they were able to control glycosuria with estrogenic substance. They attributed their results to complete suppression of the pituitary.

A year later Nelson and Overholser<sup>3</sup> reported on the effect of estrin upon experimental pancreatic diabetes in the monkey. In their animals, alternate periods of injection and withdrawal of estrin resulted in corresponding fluctuations in the urinary sugar. These investigators also attributed their results to suppression of the pituitary.

Mazer<sup>2</sup> and his coworkers, in 1935, reported that while treating menopausal patients with large doses of female sex hormone, the 3 diabetics in their series could be maintained on a reduced insulin dose. Withdrawal of estrogen was associated with a return to the original insulin requirement. A study of the blood sugar levels of normal women under similar circumstances indicated that in these patients the blood sugar level was unaffected.

The only clinical cases reported were those of Patton,<sup>4</sup> who, in 1936, demonstrated successful results with the clinical use of large doses of female sex hormone in 3 cases. One of these is worthy of note in that recurrent coma during the menstrual periods was prevented by the use of large doses of estrogenic hormone.

In our investigation we were interested in studying the effect of intramuscularly administered estrogen on the insulin requirement

of a series of diabetic women. Nine cases were taken from the Metabolic Service of Sea View Hospital. They were chosen without regard for any indication for estrogen therapy. The menstrual history of these patients, however, is of interest in that only 1 member of the group was menstruating regularly. Three had periods of amenorrhea of several months' duration and 5 had passed through the menopause.

TABLE 1.—VARIATIONS IN INSULIN DOSAGE WITH ESTROGEN (OBSERVATIONS ON 9 CASES FROM THE METABOLIC SERVICE OF SEA VIEW HOSPITAL, OCTOBER, 1938, TO OCTOBER, 1939).

Date of observation.	Units of insulin.									
	Average.	AN.	CH.	CA.	RO.	AR.	BI.	PE.	RA.	WI.
1938.	Before Estrogen.									
10/1 . . . . .	63	35	45	..	50	90	70	112	75	30
10/15 . . . . .	68	35	45	..	45	80	90	130	75	40
10/29 . . . . .	76	35	40	..	40	80	110	150	75	80
11/11 . . . . .	76	40	40	..	40	90	90	150	75	80
11/25 . . . . .	78	40	40	*	40	90	85	173	75	80
12/9 . . . . .	76	40	40	65	40	90	85	170	75	80
12/23 . . . . .	76	40	40	60	40	90	85	170	75	80
1939.	During Estrogen.									
1/8 . . . . .	76	42	40	60	40	90	85	173	75	80
1/22 . . . . .	75	42	40	60	40	90	85	180	75	80
2/7 . . . . .	84	42	40	70	40	110	90	180	80	80
After Estrogen.										
2/15 . . . . .	80	42	40	70	40	110	90	180	80	70
2/22 . . . . .	80	38	40	70	40	100	87	180	75	70
3/1 . . . . .	75	30	35	70	40	100	85	170	70	70
3/8 . . . . .	66	25	30	65	40	90	73	160	65	65
3/22 . . . . .	61	15	20	60	35	85	70	145	60	55
4/10 . . . . .	46	5	10	50	20	90	50	125	45	25
4/23 . . . . .	43	0	10	45	15	90	43	115	45	20
5/3 . . . . .	47	5	10	45	15	90	75	115	45	20
5/19 . . . . .	49	12	20	55	15	90	75	115	45	15
6/3 . . . . .	48	15	20	55	15	90	70	115	50	5
6/21 . . . . .	51	15	20	65	25	90	70	120	55	0
7/9 . . . . .	54	15	20	80	30	90	70	120	60	0
7/16 . . . . .	56	15	20	80	30	90	70	120	80	0
7/23 . . . . .	57	15	20	80	30	90	70	130	80	0
8/1 . . . . .	58	15	20	80	30	90	80	120	80	0
8/8 . . . . .	57	15	20	80	30	90	80	120	80	0
8/20 . . . . .	53	15	20	80	25	90	80	95	75	5
8/30 . . . . .	54	15	5	75	35	90	85	100	70	0
9/8 . . . . .	53	25	10	65	35	75	85	120	60	0
9/22 . . . . .	62	25	20	50	40	115	95	150	65	0
10/1 . . . . .	62	25	22	60	40	125	95	130	65	0
10/12 . . . . .	63	30	22	65	40	130	65	145	70	0

\* Prior to date of initial observation.

"Units of insulin" represents daily requirement of regular, protamine zinc or both.

The method of administration was that generally used in the treatment of the menopausal syndrome and therefore differed from that used in previous experiments where daily injections were usually given. Our patients received an intramuscular injection of 10,000 International Units of estrogenic hormone twice a week.

To determine the variations in the average insulin requirement before, during and after the administration of estrogen, the patients were followed for a period of 1 year; 4 months before estrogen, 5 months during its administration and 3 months after it had been discontinued.



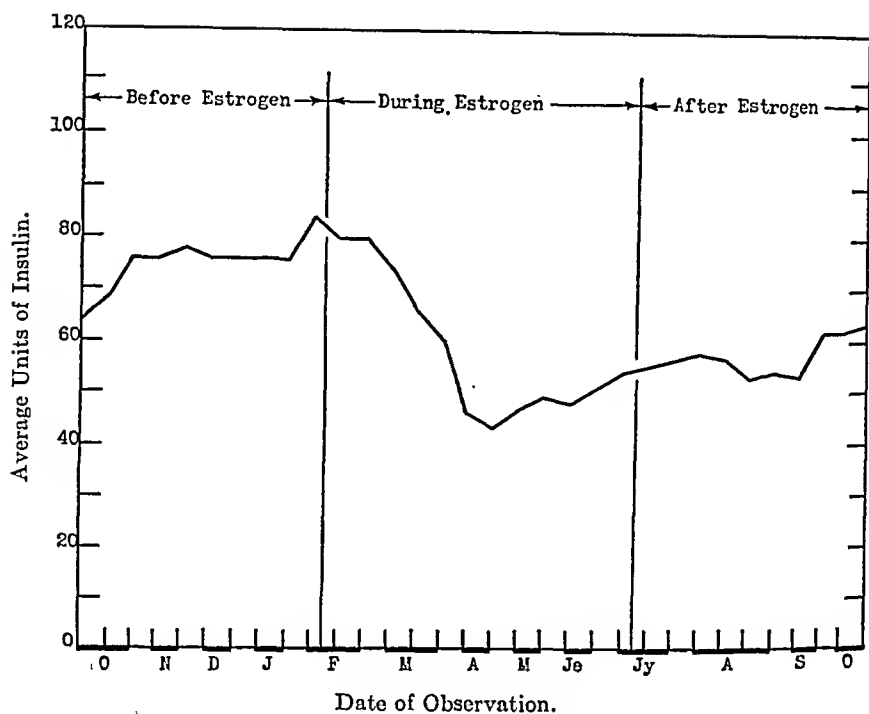


CHART 1.—Variations in average insulin dosage (regular and PZI) with estrogen.

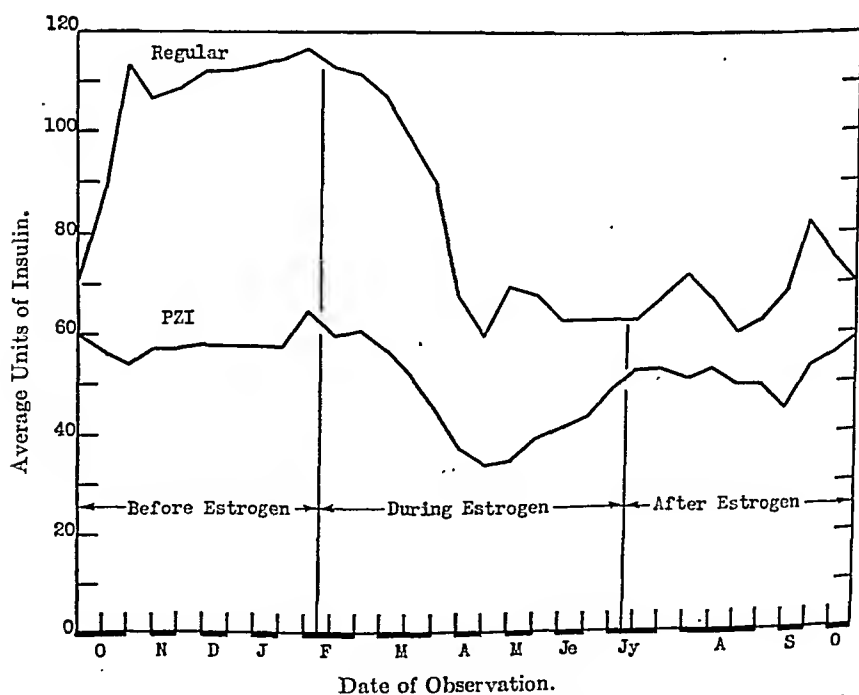


CHART 2.—Variations in insulin dosage with estrogen. Comparison of regular insulin with protamine zinc insulin.

During the first 4 months we attempted to reduce the individual insulin dose to the lowest level compatible with proper control. We took as our standards of control, a normal fasting blood sugar, a glycosuria of less than 1% with a total loss of less than 20 gm. of sugar in the 24-hour urine. At no time during this 4-month period of observation was there any indication that the average daily insulin requirement could be materially reduced. Instead it rose from 63 to 84 units daily (Table 1). Soon after estrogen was begun,

TABLE 2.—VARIATIONS IN INSULIN DOSAGE WITH ESTROGEN (OBSERVATIONS ON 9 CASES FROM THE METABOLIC SERVICE OF SEA VIEW HOSPITAL, OCTOBER, 1938, TO OCTOBER, 1939).

Date of observation.	Comparison of regular insulin with protamine zinc insulin, units of insulin.										
	Regular.				Protamine zinc.						
	WI.	PE.	BI.	Av.	Av.	RA.	AR.	RO.	CA.	CH.	AN.
1938.	Before Estrogen.										
10/1 . .	32	112	70	71	59	75	90	50	..	45	35
10/15 . .	40	130	90	87	56	75	80	45	..	45	35
10/29 . .	80	150	110	113	54	75	80	40	..	40	35
11/11 . .	80	150	90	107	57	75	90	40	..	40	40
11/25 . .	80	173	85	109	57	75	90	40	*	40	40
12/9 . .	80	170	85	112	58	75	90	40	65	40	40
12/23 . .	80	170	85	112	58	75	90	40	60	40	40
1939.	During Estrogen.										
1/8 . .	80	173	85	113	58	75	90	40	60	40	42
1/22 . .	80	180	85	115	58	75	90	40	60	40	42
2/7 . .	80	180	90	117	64	80	110	40	70	40	42
2/15 . .	70	180	90	113	60	80	110	40	70	40	42
2/22 . .	70	180	87	112	61	75	100	40	70	40	38
3/1 . .	70	170	85	108	58	70	100	40	70	35	30
3/8 . .	65	160	73	99	53	65	90	40	65	30	25
3/22 . .	55	145	70	90	46	60	85	34	60	20	15
4/10 . .	25	125	50	67	37	45	90	20	50	10	5
4/23 . .	20	115	45	60	34	45	90	15	45	10	0
5/3 . .	20	115	75	70	35	45	90	15	45	10	5
5/19 . .	15	115	75	68	39	45	90	15	55	20	12
6/3 . .	5	115	70	63	41	50	90	15	55	20	15
6/21 . .	0	120	70	63	43	55	90	25	55	20	15
7/9 . .	0	120	70	63	49	60	90	30	80	20	15
7/16 . .	0	120	70	63	53	80	90	30	80	20	15
7/23 . .	0	130	70	67	53	80	90	30	80	20	15
8/1 . .	0	135	80	72	51	70	90	30	80	20	15
8/8 . .	0	120	80	67	53	80	90	30	80	20	15
8/20 . .	5	95	80	60	50	75	90	25	80	10	15
8/30 . .	0	100	85	62	50	70	90	35	75	5	25
9/8 . .	0	120	85	68	45	60	75	35	65	10	25
9/22 . .	0	150	95	82	53	65	115	40	50	20	25
10/1 . .	0	130	95	75	56	65	125	40	60	22	25
10/12 . .	0	145	65	70	59	70	130	40	65	22	30

\* Prior to date of initial observation.

however, the average daily insulin requirement began to fall so that within a period of 10 weeks it dropped from 84 to 43 units daily, representing a saving of 47% (Table 1). During the second 10 weeks of the administration of estrogen the average daily insulin requirement rose to 54 units, an increase of 11 units, but still 33% less than before estrogen was begun (Table 1). At this time estrogen was discontinued. Nevertheless the patients were followed 3 months longer. During this period the average daily insulin requirement rose to 63 units (Table 1), an increase of only 9 units

and still 21 units less than the amount used immediately preceding the beginning of estrogen (Chart 1).

TABLE 3.—VARIATIONS IN INSULIN DOSAGE WITH ESTROGEN (OBSERVATIONS ON 9 CASES FROM THE METABOLIC SERVICE OF SEA VIEW HOSPITAL, OCTOBER, 1938, TO OCTOBER, 1939).

Date of observation.	Comparison of premenopausal and postmenopausal cases, units of insulin.										
	Premenopausal.					Postmenopausal.					
	AN.	CH.	CA.	RO.	Av.	Av.	AR.	BI.	PE.	RA.	WI.
1938.	Before Estrogen.										
10/1 . .	35	45	..	50	43	75	90	70	112	75	30
10/15 . .	35	45	..	45	42	83	80	90	130	75	40
10/29 . .	35	40	..	40	38	99	80	110	150	75	80
11/11 . .	40	40	..	40	40	97	90	90	150	75	80
11/25 . .	40	40	*	40	40	101	90	85	173	75	80
12/9 . .	40	40	65	40	46	100	90	85	170	75	80
12/23 . .	40	40	60	40	45	100	90	85	170	75	80
1939.	During Estrogen.										
1/8 . .	42	40	60	40	46	101	90	85	173	75	80
1/22 . .	42	40	60	40	46	102	90	85	180	75	80
2/7 . .	42	40	70	40	48	108	110	90	180	80	80
After Estrogen.											
2/15 . .	42	40	70	40	48	106	110	90	180	80	70
2/22 . .	38	40	70	40	47	102	100	87	180	75	70
3/1 . .	30	35	70	40	44	99	100	85	170	70	70
3/8 . .	25	30	65	40	40	90	90	73	160	65	65
3/22 . .	15	20	60	35	33	83	85	70	145	60	55
4/10 . .	5	10	50	20	21	67	90	50	127	45	25
4/23 . .	0	10	45	15	18	63	90	42	115	45	20
5/3 . .	5	10	45	15	19	69	90	75	115	45	20
5/19 . .	12	20	55	15	26	68	90	75	115	45	15
6/3 . .	15	20	55	15	21	66	90	70	115	55	0
6/21 . .	15	20	65	25	31	67	90	70	120	55	0
7/9 . .	15	20	80	30	36	68	90	70	120	60	0
After Estrogen.											
7/16 . .	15	20	80	30	36	72	90	70	120	80	0
7/23 . .	15	20	80	30	36	74	90	70	130	80	0
8/1 . .	15	20	80	30	36	74	90	80	120	80	0
8/8 . .	15	20	80	30	36	74	90	80	120	80	0
8/20 . .	15	20	80	25	35	69	90	80	95	75	5
8/30 . .	15	5	75	35	33	69	90	85	100	70	0
9/8 . .	25	10	65	35	34	68	75	85	120	60	0
9/22 . .	25	20	50	40	34	85	115	95	150	65	0
10/1 . .	25	22	60	40	37	83	125	95	130	65	0
10/12 . .	30	22	65	40	39	82	130	65	145	70	0

\* Prior to date of initial observation.

"Units of insulin" represents daily requirement of regular, protamine zinc or both.

The type of insulin administered did not influence the results obtained. Table 2 indicates that during the first 11 weeks of the administration of estrogen there was a drop of 47%, from 117 to 60 units daily, in the average insulin requirement of the patients receiving regular insulin. During the same time the patients on protamine zinc insulin showed a similar saving represented by a decrease in the average daily insulin requirement from 64 to 34 units. The percentage of insulin saved in the two groups is identical, although the absolute drop in the insulin requirement is greater in the group which received regular insulin (Chart 2).

If the cases are separated into those who have passed the menopause and those who are premenopausal, it becomes evident that the decrease in the insulin requirement associated with the administration of estrogen is more pronounced in the premenopausal group.

In the younger group, the drop from an average of 48 units daily to an average of 18 units represents an insulin saving of 63%. In the older group, on the other hand, the initial average requirement of 108 units daily fell with estrogen to 63 units, a saving of 42% (Table 3). When estrogen was discontinued the younger patients were receiving an average of 36 units of insulin daily. In the succeeding 3 months their requirement rose to 39 units daily, an increase of less than 1%. In the older group, however, there was a rise in the average insulin requirement of 20% for the same period of time, from 68 to 82 units daily (Table 3). The data therefore

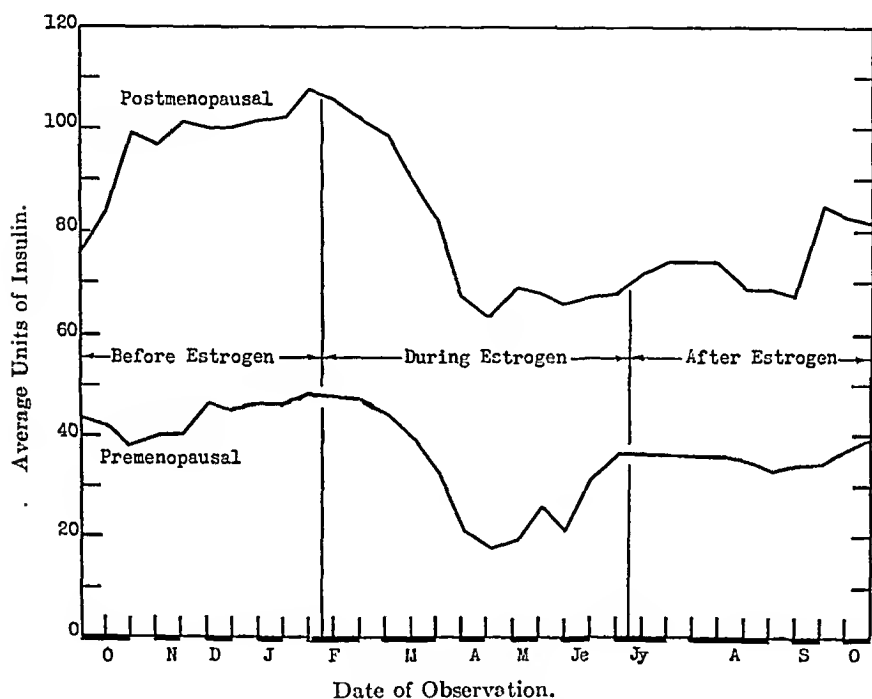


CHART 3.—Variations in insulin dosage with estrogen. Comparison of premenopausal with postmenopausal cases.

indicate that the administration of estrogen was associated with a greater and more permanent reduction in the insulin requirement in the premenopausal than in the postmenopausal group (Chart 3).

**Untoward Effects.** During the administration of estrogen we encountered several untoward effects. Some of our patients complained of severe headache starting soon after the injection and lasting 24 to 36 hours. One patient had painful, tender breasts which subsided 4 days after estrogen was discontinued. Another of our patients developed a fibroid uterus. Whether this was a coincidental development or in some way associated with the administration of estrogen is difficult to determine.

**Discussion.** In interpreting our results it is significant that all our patients, regardless of age and endocrine constitution, received the same amount of estrogenic hormone at the same time interval. A similar amount of estrogen, however, will not produce a like effect in different individuals. The results might have been more spectacular had we been able to vary the amount of estrogen administered to each patient. Because of the obvious difficulties such a task entails in a study of this type a common dose was administered to all our patients.

The mode of action of estrogen in depressing the glycosuria of the diabetic is difficult to explain. Barnes and his coworkers assumed that estrogen caused a complete suppression of the pituitary and warned that such suppression might be dangerous because it might involve atrophic changes in other organs, especially the adrenal cortex. Nelson and Overholser suggested that the effect may be due to an inhibition of the pituitary diabetogenic hormone. This explanation seems plausible, especially since the pituitary is the only gland known to have pancreatotropic and gonadotropic hormones, both of which are most likely derived from the basophil cells. Furthermore, it is significant that diabetes is often aggravated during the periods of gonadal stress, as at puberty, menstruation, pregnancy and the menopause. The *modus operandi* in the gonadopituitary-pancreatic relationship, however, is still indefinite.

It is of interest that our postmenopausal patients did not respond so well as our younger group. In the older patients the function of all anterior pituitary cells is decreased. If the action of estrogen on carbohydrate metabolism is by way of the pituitary, as we have reason to assume, we can readily understand the better results in the premenopausal group.

**Conclusions.** 1. The administration of 10,000 International Units of estrogenic hormone twice a week to a series of 9 diabetic women was associated with a diminution in their insulin requirement.

2. The average daily insulin requirement did not return to the "pre-estrogen" level even after estrogen had been discontinued for a period of 3 months.

3. The type of insulin used in the control of the diabetes had no influence on the results obtained.

4. In the premenopausal group the diminution in the insulin requirement associated with the administration of estrogen was greater and more sustained than in the postmenopausal group.

We are indebted to Roehe-Organon Company and to E. R. Squibb for our supply of estrogenic hormone.

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## THE CALCIUM AND PHOSPHORUS IN THE CEREBROSPINAL FLUID IN DIABETES INSIPIDUS.

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STUDYING the blood in a group of 26 patients with diabetes insipidus, I<sup>1</sup> found a slight but definite increase in the serum calcium in some of the cases. Because of the interest in the relation of the calcium content of the spinal fluid and blood serum and because of the similarity between the polyuria of diabetes insipidus and the polyuria which occurs in certain cases of hyperparathyroidism, the concentration of the calcium and phosphorus in the cerebrospinal fluid was studied in 10 patients with diabetes insipidus and compared with those in the blood serum. In addition, the chloride and protein contents were determined.

The general impression is that the concentration of the calcium in the cerebrospinal fluid is remarkably constant in health and disease. The calcium normally varies from 4.5 to 5.5 mg., an average of 5 mg. per 100 cc. of cerebrospinal fluid<sup>9</sup> and it represents 45 to 50% of the blood serum calcium. The phosphorus content varies from 1 to 1.5 mg. per 100 cc. and usually amounts to 38% of the serum phosphorus. McLean and Hastings<sup>7</sup> have shown that the calcium in the serum is composed of a diffusible fraction which represents about 50% of the total calcium and passes through a membrane impermeable to protein, and a non-diffusible fraction which amounts to about 50% of the total calcium and remains with the protein in the serum. They found that the diffusible calcium of the serum is all or nearly all ionized and that consequently the diffusible calcium is a measure of  $\text{Ca}^{++}$  concentrations. They made a number of observations on human cerebrospinal fluid and found that the spinal fluid contains about 5 mg. calcium per 100 cc. fluid which is all diffusible and all but an insignificant amount is in the form of  $\text{Ca}^{++}$ . They believed that the spinal fluid calcium concentration represents the diffusible or ionized portion of the serum calcium. However, there are certain diseases in which there has been reported an increase in the calcium of the cerebrospinal fluid, particularly the meningitic or other fluids with a high protein content. Cantarow<sup>2</sup> found the calcium content of 4 to 7.5 mg. per 100 cc. of cerebrospinal fluid in patients with inflammatory disease of the meninges and brain. Merritt and Bauer<sup>8</sup> also found an increase in the spinal fluid calcium in meningitis. Cohn, Kaplan, and Levinson<sup>4</sup> obtained similar results in such cases and also in cases with hydrocephalus and brain tumor, in addition to an increase in the spinal fluid phosphorus. Gregory and Andersch<sup>6</sup> found the spinal fluid calcium to be as high as 6.4 mg. per 100 cc. in 1 of 2

cases of hyperparathyroidism. This paper presents the results of the calcium, phosphorus, chloride and protein concentrations in the spinal fluid and in the blood serum of 10 patients with diabetes insipidus.

**Plan of Investigation.** The spinal fluid was obtained by lumbar puncture from 10 patients with diabetes insipidus whose ages ranged from 16 to 67 years. The criteria for the diagnosis of diabetes insipidus were a persistent daily fluid intake and output of about 8 to 14 liters for years, which were reduced to normal following the intranasal or intramuscular administration of pituitary extract (pituirrin).

There were 8 males and 2 females. The disease was idiopathic in origin in 8 cases and postencephalitic in 2, both males. The calcium was determined by the Clark and Collip modification of the Kramer-Tisdall method.<sup>3</sup> The phosphorus was determined by the method of Fiske and Subbarow.<sup>5</sup>

Having demonstrated that the distribution of calcium between  $\text{Ca}^{++}$  and Ca bound to protein depends on the total protein, McLean and Hastings<sup>7</sup> showed how to calculate the  $\text{Ca}^{++}$  concentrations from values for total calcium and total protein in serum and based on these values they made a Cartesian nomogram from which the  $\text{Ca}^{++}$  concentrations may be determined.

In this investigation the  $\text{Ca}^{++}$  concentration in the blood serum of the 10 patients with diabetes insipidus was calculated according to their nomogram and the results compared with the calcium determinations in the spinal fluid and the differences noted. Control tests were made in 10 patients with syphilis, in whom diagnostic lumbar punctures were performed.

TABLE 1.—COMPARISON OF CONCENTRATIONS OF  $\text{Ca}^{++}$  IN SERUM AND TOTAL CALCIUM IN SPINAL FLUID IN CONTROL PATIENTS.\*†

Case.	Serum.			Spinal fluid, total Ca.	Spinal fluid Ca minus serum $\text{Ca}^{++}$ .
	Total Ca.	Total protein.	Calculated $\text{Ca}^{++}$ .		
1 . . . . .	2.94	66	1.38	1.38	0
2 . . . . .	2.96	70	1.34	1.00	-0.34
3 . . . . .	2.90	70	1.32	1.15	-0.17
4 . . . . .	2.69	72	1.24	1.20	-0.04
5 . . . . .	2.63	68	1.16	1.32	+0.16
6 . . . . .	2.63	70	1.13	1.28	+0.15
7 . . . . .	2.90	75	1.27	1.40	+0.13
8 . . . . .	2.58	71	1.11	1.28	+0.17
9 . . . . .	2.74	69	1.17	1.35	+0.18
10 . . . . .	2.91	71	1.31	1.40	+0.09
Average . . .	2.79	70	1.24	1.27	+0.03

\* The calcium results are recorded in mM (millimol) per liter of water and the total protein in gm. per liter of serum.

† All the control patients were syphilitics who had been under anti-luetic treatment in the past. There was no other diagnosis.

**Results.** The results in the spinal fluid compared with those in the serum are given in the accompanying tables. In the control tests the calcium concentration of the spinal fluid ranged from 3.9 to 5.6 mg. per 100 cc. or from 1 to 1.4 mM per liter of spinal fluid, the average being 1.27 mM per liter. In the serum, the total calcium varied from 9.5 to 11 mg. per 100 cc. or from 2.58 to 2.96 mM per

liter of water, the average being 2.79 mM. The  $\text{Ca}^{++}$  concentrations of serum ranged from 1.11 to 1.38 mM per liter of water, the average being 1.24 mM. The total calcium in the spinal fluid was nearly the same as the  $\text{Ca}^{++}$  concentration of the serum, the average difference being +.03 mM per liter which corresponds with the results obtained by McLean and Hastings. In 4 cases the difference ranged from 0 to -.34 mM per liter water and in 6 cases it varied from +.03 to +.18 mM per liter.

In the patients with diabetes insipidus the results were somewhat different. The total calcium in the spinal fluid ranged from 4.2 to 7.4 mg. per 100 cc. or from 1.05 to 1.85 mM per liter, the average being 1.51 mM. In 5 of these patients, the calcium ranged from 5.8 to 7.4 mg. per 100 cc. spinal fluid or from 1.45 to 1.85 mM per liter and in one of these patients whose spinal fluid calcium was 7.4 mg. a repeat spinal fluid in 3 months gave the same result.

TABLE 2.—COMPARISON OF CONCENTRATIONS OF  $\text{Ca}^{++}$  IN SERUM AND TOTAL CALCIUM IN SPINAL FLUID IN PATIENTS WITH DIABETES INSIPIDUS.\*

Case.	Serum.			Spinal fluid, total Ca.	Spinal fluid Ca minus serum $\text{Ca}^{++}$
	Total Ca.	Total protein.	Calculated $\text{Ca}^{++}$ .		
1 . . . . .	2.76	59	1.30	1.80	+0.50
2 . . . . .	2.91	71	1.31	1.50	+0.19
3 . . . . .	3.13	72	1.36	1.45	+0.09
4 . . . . .	2.26	71	0.90	1.05	+0.15
5 . . . . .	2.71	77	1.07	1.70	+0.63
6 . . . . .	2.69	71	1.13	1.38	+0.25
7 . . . . .	2.75	72	1.13	1.40	+0.27
8 . . . . .	2.68	66	1.19	1.33	+0.14
9 . . . . .	2.95	61	1.43	1.30	-0.13
10 . . . . .	2.98	61	1.44	1.85	+0.41
10 . . . . .	3.14	60	1.52	1.85	+0.33
Average . . . . .	2.81	68	1.25	1.51	+0.26

\* The calcium results are recorded in mM (millimol) per liter of water and the total protein in gm. per liter of serum.

In the serum, the total calcium ranged from 8.4 to 11.8 mg. per 100 cc. or from 2.26 to 3.14 mM per liter of water, the average being 2.81 mM. The serum  $\text{Ca}^{++}$  values were from .90 to 1.52 mM per liter of water, the average being 1.25 mM. The total calcium of the spinal fluid was appreciably greater than the  $\text{Ca}^{++}$  concentration in the serum in a number of these cases, the average difference being +.26 mM per liter of water as compared with +.03 mM in the control tests. In only one of these cases was the difference on the minus side. In the remaining cases, 4 had a difference of +.09 to +.19 mM per liter of water and 6 had a difference of +.25 to +.63 mM per liter. The ratio of the spinal fluid calcium to the serum calcium ranged from 47 to 69%.

The phosphorus content of the spinal fluid and serum was within the normal limits and the values were much the same as in the control tests.



An elevated total protein of from 64 to 150 mg. per 100 cc. spinal fluid appeared in 3 cases, 2 of which were associated with post-encephalitic Parkinson's syndrome. The serum protein determinations were normal.

TABLE 3.—COMPARISON OF FINDINGS IN SPINAL FLUID AND SERUM IN PATIENTS WITH DIABETES INSIPIDUS AND IN CONTROL PATIENTS.\*

Case.	Diabetes insipidus.				Control tests.		
	Total Ca.	P.	Cl.	Total protein.	Total Ca.	P.	Total protein.
1 CSF	7.2	1.6	448	90.0	5.5	2.4	35.0
1 Serum	10.4	5.0	318	5.9	11.0	4.1	6.6
2 CSF	6.0	1.2	461	64.0	3.9	2.1	30.0
2 Serum	10.8	3.8	394	7.1	11.0	...	7.0
3 CSF	5.8	1.6	442	150.0	4.6	1.9	40.0
3 Serum	11.6	4.4	335	7.2	10.7	...	7.0
4 CSF	4.2	1.0	467	30.0	4.7	1.7	5.0
4 Serum	8.4	3.2	412	7.1	10.0	3.7	7.2
5 CSF	6.8	1.8	...	18.0	5.3	1.8	80.0
5 Serum	10.0	3.6	...	7.7	9.8	...	6.8
6 CSF	5.5	...	...	...	5.1	1.9	35.0
6 Serum	10.0	3.7	421	7.1	9.8	3.5	7.0
7 CSF	5.6	1.6	404	15.0	5.6	1.7	35.0
7 Serum	10.2	3.9	375	7.2	10.7	2.7	7.5
8 CSF	5.3	2.7	382	37.0	5.1	1.7	20.0
8 Serum	10.0	4.1	339	6.6	9.5	3.6	7.1
9 CSF	5.2	1.2	492	30.0	5.4	1.6	20.0
9 Serum	11.1	3.8	314	6.1	10.2	3.8	6.9
10 CSF	7.4	1.6	451	41.0	5.6	1.6	30.0
10 Serum	11.2	4.0	357	6.1	10.8	4.3	7.1
10 CSF	7.4	...	448	13.0			
10 Serum	11.8	2.6	346	6.0			

\* The results are expressed in mg. per 100 cc. except the serum protein, which is recorded in gm. per 100 cc. CSF indicates cerebrospinal fluid; P, phosphorus, and Cl, chloride.

The chloride concentration in the spinal fluid varied from 382 to 492 mg. per 100 cc. in these cases, the normal being approximately 440 mg. The chloride in the blood was within the normal range.

**Comment.** The cerebrospinal fluid has been of special interest because it has been regarded by certain investigators as normally a protein-free filtrate of the blood plasma and that its calcium content represents the diffusible or ionized calcium of the blood or approximately one-half of the total blood calcium concentration. Furthermore, the calcium content of the blood and spinal fluid is maintained at a markedly constant level. The results of this investigation indicate that there is a disturbance in the calcium level in some cases with diabetes insipidus. The average spinal fluid calcium concentration of 1.51 mM per liter was slightly greater than the average serum  $\text{Ca}^{++}$  values of 1.25 mM per liter of water as calculated from the total calcium and protein in the serum, according to the method described by McLean and Hastings. The average difference was +.26 mM per liter of water and the greatest difference was +.63 mM. This was in contrast to the control tests in which the average spinal fluid calcium was 1.27 mM per liter and the average serum  $\text{Ca}^{++}$  values of 1.24 mM per liter of water, an average difference of only

+0.03 mM per liter of water. The cause for this is conjectural. The serum calcium varies with the serum protein. However, on this basis the spinal fluid calcium would not be increased because its protein content is so small that it would not appreciably alter its calcium concentrations. The fluids of the human body, including both protein-free and protein containing fluids, contain a small but appreciable amount of a bound but diffusible form of calcium. According to McLean and Hastings, this amount has been estimated to be of the order of magnitude of 0.15 mM per kilo of water. Possibly, in some of the cases of diabetes insipidus, the excess of the calcium of the spinal fluid over the calculated  $\text{Ca}^{++}$  concentrations of the serum may be due to an increase in the amount of bound but diffusible form of calcium. Whether or not such an explanation is correct must await direct determination of the  $\text{Ca}^{++}$  concentration of cerebrospinal fluid in comparable cases.

**Summary.** The concentrations of the calcium, phosphorus, chlorides and protein were studied in the spinal fluid and blood serum in 10 patients with diabetes insipidus.

The average concentration of the spinal fluid calcium was slightly greater than that of the  $\text{Ca}^{++}$  content of the serum (1.51 *vs.* 1.27 mM per liter) in these patients. A series of control patients showed no such difference between their serum  $\text{Ca}^{++}$  concentrations and cerebrospinal fluid calcium (1.27 *vs.* 1.24 mM per liter).

Analyses for inorganic phosphate, chloride and protein showed no significant differences.

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## MAINTENANCE OF NITROGEN EQUILIBRIUM OF AMINO ACIDS ADMINISTERED PARENTERALLY.

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THE maintenance of an adequate state of nutrition in surgical and medical patients where enforced fasting is unavoidable can be accomplished by parenteral feeding. Glucose infusions contribute

the necessary fluid requirement as well as calories for energy. However, the continuous destruction of body proteins necessitates the administration of protein for replacement. Proteins foreign to the human body and dissimilation products of protein as far down as peptones cannot be administered parenterally because they produce anaphylactic reactions. However, amino acids do not cause such reactions when given parenterally.

Abderhalden,<sup>1</sup> in 1909, was able to maintain nitrogen balance by feeding digested lean beef per rectum. McClendon, Cavett and Johnson<sup>4</sup> more recently were able to maintain nitrogen balance by the administration of amino acids per rectum. Elman<sup>3</sup> was the first to administer intravenous infusions of amino acids to man clinically. He demonstrated that nitrogen balance could be achieved by giving a mixture of amino acids<sup>2</sup> as the only source of nitrogen.

The following study was undertaken: 1, to find whether or not a mixture containing the essential amino acids might be administered to patients without untoward reactions; 2, to determine the best possible method of its administration; and 3, to determine whether patients given this mixture can convert the amino acids to body protein and can be kept in nitrogen balance.

The mixture of amino acids used in this investigation was prepared by one of us (M. S.). It is a hydrolysate of casein to which has been added 1.8% tryptophan and 1.5% cystine. It contains 1.0% nitrogen, 5.0% glucose, traces of calcium ions, 0.015% potassium chloride, and 0.7% sodium chloride. It is a clear, amber-colored fluid with a distinct smell of meat broth. Determinations show it to contain about 7 gm. amino acid nitrogen per 100 cc. It is sterile in aerobic and in anaerobic culture.

To determine whether this mixture could be given without anaphylactic reaction, 2 rabbits were injected intramuscularly with 5 cc. of the fluid three times at 6-day intervals and did not show any symptoms when reinjected intravenously after 21 days with 1 cc. and 2 cc. respectively. Thirty-five cubic centimeters of the fluid given subcutaneously to 2 rabbits was tolerated without reaction and was absorbed within 7 hours. Chemical tests for protein as well as polypeptides and albumoses were negative (sulphosalicylic acid, biuret reaction).

Subsequently, 13 patients were injected with the amino acids mixture. The patients selected had no diseases which might affect the protein metabolism, such as diseases of the liver or kidneys, diabetes mellitus, carcinoma, or infections. The patients chosen were orthopedic cases and postoperative cases in the Department of Gynecology. Five of these persons were under observation for 3 to 5 weeks and received daily subcutaneous infusions of 500 to 600 cc. of the amino acids mixture during the experimental period, each of which was 1 week long. Four patients received 1 to 300 cc. intravenously in amounts increasing daily. Four received daily intra-

venous injections of 500 to 750 cc. and were under observation for from 18 to 21 days. Thus, there were 5 patients who received the amino acids mixture subcutaneously and 8 who received it intravenously.

TABLE 1.—NITROGEN BALANCE FIGURES (DAILY AVERAGES) DURING PARENTERAL ADMINISTRATION OF AMINO ACIDS AND IN CONTROL PERIOD.

Case number.	Period.	Intake.					Output.		Amino acid-N utilized, gm.
		Protein, gm.	Protein nitrogen, gm.	Amino acid, cc.	Amino acid nitrogen, gm.	Total nitrogen, gm.	Total nitrogen, gm.	Amino acid nitrogen, gm.	
1	Control	60	9.6			9.6	8.20	2.49	4.70
	Experimental	20	3.2	500	5.0	8.2	11.91	2.79	
2	Control	80	12.8			12.8	7.61	1.50	4.75
	Experimental	40	6.4	600	6.0	12.4	10.88	2.75	
3	Control	60	9.6			9.6	5.10	1.45	4.13
	Experimental	20	3.2	500	5.0	8.2	6.63	2.32	
4	Control	70	11.2			11.2	7.26	1.70	4.50
	Experimental	30	4.8	500	5.0	9.8	7.84	2.20	
5	Control	65	10.4			10.4	9.30	1.55	5.35
	Experimental	25	4.0	600	6.0	10.0	8.01	2.20	
6	Control	70	11.2			11.20	7.33	1.80	4.14
	Experimental	38	6.8	500	5.0	11.08	8.00	2.66	
7	Control	65	10.40			10.40	7.60	1.28	3.91
	Experimental	33	5.28	500	5.0	10.28	7.58	2.37	

For 7 days before the experimental period the patients were given a high carbohydrate diet of 45 to 60 calories and 1.0 gm. of protein per kg. of body weight. The urines were collected throughout each 24-hour period. Determinations of the total nitrogen (by Nesslerization), urine amino acids (by the method of Folin as modified by Sahyun<sup>5</sup>), creatine and creatinine were made daily. The nitrogen contents of the stools were not determined. Since none of the patients had a diarrhea during the investigation, the nitrogen contents of the stools were considered to be 1.0 to 2.0 gm. per day. In the orthopedic patients studied, after 7 days of control period, part of the food protein was replaced by a corresponding amount of amino acids mixture for the following 7 days. The same urine studies were made daily. Thereafter a second control period similar to the first followed.

The injections were uniformly well tolerated. The mixture was diluted with an equal amount of sterile water which had been warmed to body temperature. The time required for the injection of 1000 cc. of fluid was gauged to the comfort of the patient; it usually was 4 to 5 hours. The resorption time was found to be up to 12 hours.

Tables 1 and 2 show the results obtained with 9 patients. The figures represent averages of the daily determinations for each patient during each period.

TABLE 2.—NITROGEN BALANCE FIGURES DURING PARENTERAL ADMINISTRATION OF AMINO ACIDS TO 2 PATIENTS AFTER OPERATION.

Case number.	Period.	Diet.		Blood transfusion.		Amino acids.		Total nitrogen intake.	Urine output.		
		Protein, gm.	Nitrogen, gm.	Protein, gm.	Nitrogen, gm.	Amount, cc.	Nitrogen.		Total nitrogen.	Amino acid nitrogen.	Creatine.
8	Exp. 8 days	..	..	..	..	500	5.0	5.0	8.58	2.8	679 1st 4 days 143 2d 4 days
	Control 4 days	..	..	..	..	..	..	..	3.96	2.25	71
	Control 6 days	20.3	3.23	..	..	..	..	3.23	3.68	1.9	92
9	Control 2 days	2.21	0.35	..	..	..	..	0.35	1.56	1.2	214
	Exp. 6 days	2.94	0.47	22.62	3.62	500	5.0	9.09	1.38	1.1	94
	Exp. 6 days	1.36	0.20	22.62	3.62	750	7.5	11.32	3.02	1.5	139
	Control 4 days	19.47	3.09	..	..	..	..	3.09	3.63	1.8	132

**Case Reports.** CASE 1.—Male, aged 60, was studied for 5 weeks. Following three control periods of one week each, subcutaneous injections of 500 cc. of the amino acids mixture were given daily for 7 days. This was followed by another control period of 7 days. The average total urine nitrogen output of the experimental period was 3.7 gm. higher than the average during the control periods. The amino acid nitrogen output during the experimental period showed a surplus of 0.3 gm. compared to the control periods. This means that about 6% of the injected mixture spilled over into the urine and that 94% (4.7 gm. N) was utilized daily. The urine creatine and creatinine showed no significant difference between the control and the experimental periods and the patient's weight remained constant.

CASE 2.—Male, aged 65, was studied for 3 weeks. Subcutaneous injections of 600 cc. of the amino acids mixture were given daily for 7 days after a control period of 8 days, and this was then followed by a second control period of 7 days. The average amino acid nitrogen spilled during the experimental period was 1.25 gm. more than that spilled during the control periods. This amount represents 20.8% of the amino acids intake; the remaining 79.2% (4.75 gm. N) was utilized. The daily output of nitrogen in the urine was below the intake of 12.4 gm. The creatine output varied from an average of 56 mg. daily during the control periods to 105 mg. during the experimental period. This indicated the loss of some body protein during the period of injections.

CASE 3.—Male, aged 75, was studied for 5 weeks. There were two experimental periods of 7 days each during which daily subcutaneous injections of 500 cc. were given, and there were three control periods of 7 days each

alternating with the experimental periods. The average amino acid nitrogen spilled during the experimental periods was 0.87 gm. more than the average spilled during the control periods. Therefore, 82.6% (4.13 gm. N) of the amino acids mixture was utilized. The average creatine and creatinine output in the urine was essentially the same throughout the periods of study. This excludes the possibility of any loss of body protein. The patient's weight increased from 54.5 kg. at the start to 59.3 kg. at the end of the study.

CASE 4.—Male, aged 28, was studied for 5 weeks. There were two experimental periods of 7 days each alternating with 3 control weeks. The average amino acid nitrogen spilled during the experimental periods was 0.5 gm. (10%) more than the average during the control periods, indicating that 90% of the amino acid nitrogen injected was utilized. The average urine creatine and creatinine output was essentially the same throughout the periods of study. The patient's weight increased from 68.6 kg. to 73.0 kg. during the study.

CASE 5.—Male, aged 51, studied for 3 weeks. There was an experimental period of 7 days preceded by and followed by a control week. During the experimental period 600 cc. of the amino acids mixture was given subcutaneously. The average amino acid nitrogen spilled during the experimental period was 0.65 gm. more than during the control periods. This was about 10% of the amino acid injected, indicating that 90% of the mixture was utilized. The average urine creatine and creatinine output was the same during the control and the experimental periods. The patient's weight remained the same.

CASES 6 and 7.—Two normal men who were given 500 cc. of the amino acids mixture intravenously. They were studied for 3 weeks—one experimental week with a week before and one after as controls. Case 6 showed an average amino acid nitrogen surplus during the experimental period of 0.86 gm., or 17% of the total amino acids mixture intake. Therefore, 83% (4.14 gm. N) of the amino acid injected was utilized. The patient was in good nitrogen balance. The urine creatine and creatinine remained the same throughout the studies. The patient's weight remained the same.

Case 7 showed an average amino acid surplus of 1.09 gm. during the experimental period. This was 22% of the amino acids mixture injected, indicating that 78% (3.91 gm. N) was utilized. The patient was in nitrogen balance and the urine creatine remained the same throughout the studies.

CASES 8 and 9.—These were 2 postoperative cases who were given intravenous infusions of the amino acids mixture. Case 8 was a woman with paralytic ileus of 6 days' duration before the injections were begun. No food was given by mouth; the patient received only 5% glucose in saline. Amino acids mixture (500 cc.) was given daily for 8 days. A control period of 4 days without food followed, and then a second control period of 6 days during which she took a diet containing 20.3 gm. protein. The amino acid nitrogen output during the experimental period was 0.75 gm. (or 15% of the total injected) more than during the control period with food, and 0.55 gm. more than during the period without food. Therefore, 85% of the amino acids mixture was utilized comparing the experimental period with the food period, and 89% comparing the experimental period with the control period without food. The creatine output in the urine, which was very high at the beginning of the study (600 to 1000), showed an abrupt decrease after 4 days of the injections. The patient was very toxic at the beginning of the study.

Case 9, the second postoperative case, was a female, aged 45, who had had a total hysterectomy. About 5 weeks later a cul-de-sac abscess was opened. Two days after this the amino acids mixture injections were begun. She was given 500 cc., diluted with distilled water to 1000 cc., in-

travenously every day for 6 days. She continued to have a high temperature, was vomiting and unable to retain food. She was then given intravenously 750 cc. of amino acid, diluted with an equal amount of distilled water, daily for 6 days.

Comparing the amino acid nitrogen output of the experimental with that of the control periods, there was no increased spill of amino acids. This means that all of the amino acids were utilized. The creatine in the urine decreased rapidly after the first control period of 2 days, in spite of a febrile period during the experimental periods, indicating that little body protein needed to be utilized when amino acids were administered.

**Conclusions.** 1. A mixture of amino acids containing all the essential amino acids has been prepared which can be administered to normal and postoperative patients subcutaneously or intravenously without untoward reactions.

2. Both subcutaneous and intravenous methods of injection were found to be efficient.

3. The parenteral administration of amino acids mixture could be substituted for protein in the diet to maintain the patient in nitrogen balance. In postoperative cases where food intake is not possible, the amino acid mixture was almost completely utilized and aided toward maintaining a nitrogen equilibrium.

The possibility of using these mixtures in other kinds of clinical conditions where peroral nutrition is not possible is to be investigated.

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### VITAMIN C NUTRITION IN PELLAGRA.

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**PATHOLOGIC** states due to vitamin deficiency may be the result of the absence from the diet of one or of several essential substances.

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A multiple hypovitaminosis is probably more common than are beriberi, pellagra, or scurvy. Even these definite syndromes may be complicated by the deficiency of some other vitamin than the one primarily responsible for the disease. The diet of patients with pellagra in our clinic appeared to be extremely low in ascorbic acid. A similar observation has been reported by Spies.<sup>5</sup> It seemed likely that a deficiency of vitamin C would be of frequent occurrence in pellagra. Eighteen patients with this syndrome were accordingly studied in regard to the state of vitamin C nutrition. The amount of ascorbic acid in the blood plasma in the postabsorptive state was determined in each individual. An intravenous tolerance test was performed in 10 instances and an oral tolerance test in 4 others.

**Method.** The intravenous tolerance test was carried out as follows: The level of ascorbic acid in the plasma was determined before the intravenous administration of 1 gm. of crystalline ascorbic acid,\* and at 20 minutes, 2, 4, and 6 hours following this administration. The urinary excretion in the subsequent 5 hours was likewise measured as suggested by Wright.<sup>7</sup> The oral tolerance test was performed as described by Goldsmith and Ellinger:<sup>2</sup> 600 mg. of ascorbic acid were given by mouth, the amount excreted in the urine in the subsequent 6 hours measured, and the level in the blood determined at the end of 1 and of 3 hours. The ascorbic acid in the blood was determined by the method of Farmer and Abt,<sup>1</sup> that in the urine by titration with 2-6-dichlorophenol-indophenol after acidification with glacial acetic acid.<sup>2</sup>

Of the 18 patients in this series, 12 had severe pellagra with characteristic glossitis and dermatitis, lesions of the alimentary and genito-urinary tracts, and manifestations of central nervous system disturbance. Three patients had glossitis and dermatitis of mild degree; 2 showed only the characteristic dermatitis; and 1 only the mucous membrane lesions, including glossitis, proctitis, and vaginitis, all of which were severe. In one instance, pellagra was complicated by a chronic gastric ulcer, in another by Parkinson's syndrome. In no case was a history of chronic alcoholism obtained. The diet, in most instances, had consisted largely of rice, red beans, cereals, milk, occasional salt meat and turnip greens; fresh fruit, vegetables, and fresh meat were rarely included.

The amount of ascorbic acid in the blood during fasting varied from 0.05 to 1.15 mg. per 100 cc. (Table 1). The average of the determinations in 17 cases (1 specimen lost) was 0.29 mg. Chart 1 shows the distribution of the findings. Less than 0.4 mg. of ascorbic acid per 100 cc. of blood, the minimal level which may be considered normal, was found in 13 instances. Eleven of these values occurred in persons with severe pellagra, 1 in the patient with lesions limited to the mucous membranes, and 1 in a relatively mild pellagrin. Two individuals showed a normal amount of vitamin C in the blood; that is, 0.74 and 1.15 mg. per 100 cc. Both had mild pellagra of short duration.

\* Ascorbic acid supplied by Merck & Co.



The results obtained with the intravenous tolerance test corroborated in most instances the findings obtained on examination of the blood during fasting. A tolerance test, however, gives a much

TABLE 1.—INTRAVENOUS AND ORAL TOLERANCE TESTS OF VITAMIN C NUTRITION IN PATIENTS WITH PELLAGRA.

Vitamin C content after intravenous administration of 1000 mg. of ascorbic acid.

Case No.	Ascorbic acid in blood (fasting), mg. per 100 cc.	Blood, mg. per 100 cc.				Urine output, mg. in 5 hrs.
		20 min.	2 hrs.	4 hrs.	6 hrs.	
1	0.09	6.10	2.52	1.12	0.50	221.0
2	0.12	7.81	1.66	0.84	0.44	
3	0.32	9.45	3.25	1.46	1.01	584.0
4	0.17	6.87	2.97	2.02	0.65	410.0
5*	0.09	6.50	3.91	1.54	1.32	122.6
6	0.22	8.10	1.54	0.97	0.92	261.0
7	0.27	...	1.98	1.60	..	228.0
8	..	11.67	3.66	1.61	1.94	528.0
9	0.17	6.32	1.70	0.65	0.61	100.0
10	0.41	12.25	4.66	1.89	1.45	322.0

Vitamin C content after oral administration of 600 mg. of ascorbic acid.

		Blood, mg. per 100 cc.				Urine output, mg. in 6 hrs.
		1 hr.	2 hrs.	3 hrs.	6 hrs.	
11	0.74	1.99	..	2.72	2.00	27.0
12	0.09	0.27	..	0.40	0.50	2.60
13	1.15	..	2.11			
14	0.05	0.06	..	0.05	0.12	0.62
15	0.35					
16	0.04					
17	0.42					
18	0.19					

\* Prior to test 300 mg. of ascorbic acid was given daily by mouth for 10 days.

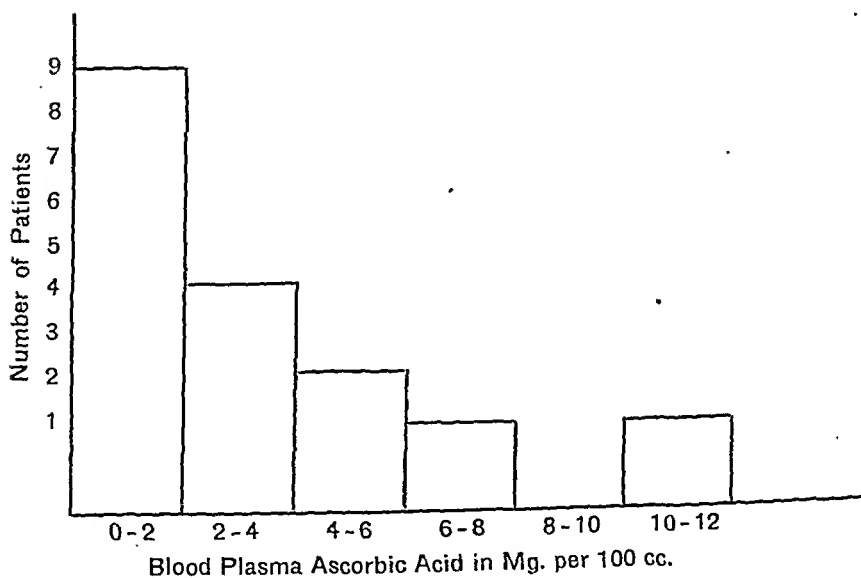


CHART 1.—Ascorbic acid in blood plasma in pellagra.

more satisfactory index of the degree of saturation of the tissues with vitamin C than does a single examination of the blood.

The response to the intravenous dose of vitamin C may be determined by measuring the excretion in the urine during a 5-hour period or by examination of the blood at intervals for 4 hours. It is our opinion that evaluation is more accurate if both the urine and blood are studied. In the presence of kidney damage, excretion of ascorbic acid may be delayed, with consequent retention in the blood.<sup>6</sup> A low renal threshold for ascorbic acid could lead to excessive output of this substance.<sup>4</sup> In either of these circumstances, determination of the ascorbic acid in the urine alone would lead to erroneous conclusions. Wright<sup>7</sup> and Portnoy and Wilkinson<sup>3</sup> have found that a normal response to the administration of 1 gm. of ascorbic acid by vein is the excretion of 400 mg. or more in the urine in 5 hours. Our studies are in agreement with these observations. Portnoy and Wilkinson<sup>3</sup> reported that the average levels of ascorbic acid in the blood in 10 normal persons after getting 1 gm. intravenously were 10.12 mg. per 100 cc. at 18 minutes, 2.76 mg. per 100 cc. at 2 hours, and 1.55 mg. per 100 cc. at 4 hours. The findings in 24 tests performed by us, 10 of which are reported here, have led us to conclude that when vitamin C nutrition is normal, the ascorbic acid in the blood rises to more than 7.0 mg. per 100 cc. in 20 minutes, remains above 2.5 mg. per 100 cc. at the end of 2 hours, and above 1.6 mg. per 100 cc. at the end of 4 hours.

The results of the intravenous tolerance test in 10 patients with pellagra (Table 1) indicated, as judged by excretion of ascorbic acid in the urine, a normal state of nutrition in 3 instances (Cases 3, 4, 8), an abnormal one in 6. The amount of ascorbic acid in the blood during fasting was subnormal in 2 tests in which the urinary excretion was normal (Cases 3, 4). This could be explained by recent inadequacy of the diet or failure of absorption from the intestinal tract of short duration, so that the stores in the body were not yet depleted. It is recognized that the level of vitamin C in the blood falls rapidly when the daily supply is diminished. The results of the intravenous tolerance tests, as judged by changes in the amount of ascorbic acid in the blood, indicated a normal state of vitamin C nutrition in 4 instances, a deficiency in 6. In Case 10, the urine value was at variance with what would be expected in view of the blood values. It is our opinion that subnormal ascorbic acid excretion in the urine in this case was due to inadequate fluid intake, since only 92 cc. of urine was excreted in 5 hours. Mild renal damage was not completely excluded as a causative factor. Nevertheless, the studies of the ascorbic acid in the blood were accepted as indicating a normal degree of saturation of the tissues with vitamin C in this individual.

An oral tolerance test was carried out in 4 patients with pellagra. When vitamin C nutrition is normal, the ascorbic acid in the blood

increases to 2.0 mg. per 100 cc., or more, 1 to 3 hours after giving 600 mg. by mouth, and the excretion in the urine is greater than 50 mg. in 6 hours. Two of the 4 patients (Cases 11, 13) were normal in regard to vitamin C nutrition, as judged by these criteria. In Case 11 there was evidence, from both clinical and laboratory standpoints, of diminished renal function, explaining the small quantity of ascorbic acid excreted in the urine when the level in the blood was well above 2.0 mg. per 100 cc.

In summary, a normal degree of tissue saturation with vitamin C was found in only 6 of 14 patients with pellagra, in whom intravenous or oral tolerance tests were performed.

The importance of recognizing multiple vitamin deficiency and of instituting adequate treatment is illustrated by 3 persons who were studied 3 to 6 months after recovery from pellagra. One returned to the hospital complaining of weakness, anorexia, and loss of weight. The second had vague gastro-intestinal complaints, and the third had purpuric areas in the skin. All 3 of these patients were found to have a vitamin C deficiency. The level of ascorbic acid in the blood during fasting was less than 0.2 mg. per 100 cc. in each case. An intravenous tolerance test in 2 of the patients and an oral tolerance test in the third indicated a marked deficiency of vitamin C (Table 2). There was rapid clinical improvement in each instance when a diet high in vitamins was instituted, supplemented by ascorbic acid, 200 to 300 mg. daily.

TABLE 2.—INTRAVENOUS AND ORAL TOLERANCE TESTS OF VITAMIN C NUTRITION IN PATIENTS WHO RECOVERED FROM PELLAGRA AND SUBSEQUENTLY DEVELOPED VITAMIN C DEFICIENCY.

Case No.	Ascorbic acid in blood (fasting), mg. per 100 cc.	Vitamin C content after intravenous administration of 1000 mg. of ascorbic acid.				
		Blood, mg. per 100 cc.				Urine output, mg. in 5 hrs.
		20 min.	2 hrs.	4 hrs.	6 hrs.	
19	0.11	8.45	2.00	1.35	0.40	170.21
20	0.17	2.52	2.26	1.65	1.64	272.00
Vitamin C content after oral administration of 600 mg. of ascorbic acid.						
Case No.	Ascorbic acid in blood (fasting), mg. per 100 cc.	Blood, mg. per 100 cc.		Urine output, mg. in 6 hrs.		
		2 hrs.				
21	0.04	0.86		0.85		

**Summary.** The state of vitamin C nutrition was studied in 18 patients with pellagra. An ascorbic acid deficiency was found in 8 of 14 patients on whom intravenous or oral tolerance tests were performed. Four additional pellagrins showed less than the normal amount of ascorbic acid in the blood during fasting. Three persons who had recovered from pellagra and who later presented symptoms suggestive of a deficiency state were found to have a depletion of the vitamin C stores of the body.

**Conclusion.** Pellagra is often accompanied by a vitamin C deficiency. The therapeutic regimen in this condition should include a diet adequate in all the essential food factors, supplemented by ascorbic acid when a deficiency of this substance is demonstrated.

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### COMPARATIVE STUDY OF THE BOERNER-LUKENS COMPLEMENT FIXATION TEST.

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EVEN the casual reader of current medical literature is forced to note the large number of "new" serologic procedures, as well as modifications of accepted procedures which are more or less constantly appearing. While many of these are described as "new," those familiar with serology will recognize that, in the last analysis, all the various complement fixation and flocculation procedures at present in use, and those proposed for use, as well as their modifications must necessarily, if they are to prove safe as well as efficient, rest upon the broad basic principles established by the laborious studies of a host of investigators.

Practically every "new" procedure advanced makes its appearance on one of two grounds, rapidity or simplicity in its performance. While these, in themselves, are desirable, they cannot—and should not—be regarded as the ultimate in desirability nor the sole nor even the outstanding criteria governing unquestioning acceptance. This should be emphasized, for it may well be feared that, to some extent, the fact that a serologic procedure is proclaimed as exceptionally rapid or essentially simple in its technical requirements has led—or may well lead—to its adoption and performance by those not always basically well prepared to assume the responsibility for the serologic diagnosis of syphilis. This is particularly true because of the present general interest in this disease and should be remarked upon and guarded against in order to lessen, as far as may be, the otherwise inevitable and—for the patient—disastrous aftermath.

Neither the competent clinician, the syphilographer nor the serologist will deny that the positive serologic reaction—when properly controlled and in competent hands—constitutes the most delicate and constant *single* symptom of syphilis. On the other hand, neither will they deny that when incompetently carried out, improperly interpreted or clinically misapplied the single serologic report constitutes the greatest single menace to both the recognition and the management of this disease.

Rapidity and relative technical simplicity are desirable assets, especially where the number of tests to be made is large. But it may again be said that they should not constitute *per se* the sole, nor even the outstanding criteria for the acceptance of a particular procedure.

The all-important criteria are only to be determined by the comparison of a new technique under proper control with methods which the test of time and trial have shown to be of acceptable delicacy and specificity.

Among the more recent modifications of the complement fixation test for syphilis is that proposed by Boerner and Lukens,<sup>1</sup> the advantages of which it is claimed include reduction in the time and labor required to set up and complete the test, and ready detection and avoidance of technical errors as well as sensitivity equal to procedures generally recognized and accepted, if not superior to some in general use.

Being among those who are firmly convinced that the safe and satisfactory serologic study of syphilis should include the application of both a complement fixation test and a flocculation test to each serum under study; recognizing that the acceptable complement fixation procedures in common use involve the expenditure of both time and labor; and recognizing also, that under some circumstances—as in boards of health, for example—time and labor are often factors of decisive importance, we were interested in the Boerner-Lukens procedure and determined to subject it to comparative trial.

It is unnecessary to add to the length of this communication by including a description of the minutia of the Boerner-Lukens method which is fully described in their original paper.

It is the purpose of this communication to report the results of its comparative trial in 1000 routine, unselected sera subjected at the same time to the Kolmer quantitative complement fixation test and the Kline flocculation test, both of which constitute the routine procedure of these laboratories.

While Boerner and Lukens describe both a qualitative and quantitative method, we chose to compare the quantitative method, for several reasons.

In the first place, our routine complement fixation is a quantitative test; in the second place, we have long been convinced by

extensive experience that the quantitative complement fixation report is of definite clinical value and utility. In fact, we are convinced that this point need no longer be labored.

The sera utilized in this study were from various sources: (a) sera routinely tested from cases from the wards and clinics of the Atlantic City Hospital; (b) sera from the Municipal Hospital Venereal Disease Clinic, many being known cases of syphilis under treatment; (c) sera from the Atlantic County Hospital for Mental Diseases.

In all 1000 sera were tested by all 3 procedures (Kolmer quantitative and Boerner-Lukens complement fixation tests and the Kline diagnostic flocculation test).

Before discussing the actual results of the comparison it may be said that, as compared to the Kolmer quantitative procedure, the Boerner-Lukens method is economical in the time required to set up an equal number of tests. It is also claimed for the latter method that, because, through consolidation of various constituents of the test, the volumes measured are relatively large, as a result, technical errors are lessened and, because of the equal volume in all tubes, if present are readily detected.

The latter is also true of the Kolmer test and, in the last analysis, as long as technical manipulations in complement fixation tests should always be governed by concentrated cerebration—as we believe to be the case—these factors, while valuable, are, after all, of relatively minor importance.

The important factors are the relative delicacy and sensitivity of the various procedures.

While comparative studies are commonly presented in tables and graphs—and, perhaps, best so presented—we believe that the salient features of the present study are evident from the brief summations below at the saving of considerable space:

Kolmer positive reactions in 1000 sera: 16.7%

Kline positive reactions in 1000 sera: 15.4%

Boerner-Lukens positive reactions in 1000 sera: 17.3%

Percentage agreement between Kolmer and Kline: 91.3%

Percentage agreement between Kolmer and Boerner-Lukens: 84.9%

Percentage agreement between Boerner-Lukens and Kline: 87.1%

The quantitative comparison between the complement fixation tests, both set up with 5 test doses of serum, was as follows:

In 83% of the positive reactions both tests showed fixation in the same number of tubes; in 17% the number of tubes showing fixation varied as shown below:

	Kolmer positive (167).	Boerner-Lukens positive (173).
Fixation in 5 tubes . . . . .	36	78
Fixation in 4 tubes . . . . .	30	33
Fixation in 3 tubes . . . . .	53	37
Fixation in 2 tubes . . . . .	32	17
Fixation in 1 tube . . . . .	16	8

From this it would appear that while the number of very strongly positive (5-tube fixation) was greater by the Boerner-Lukens test, there were more weakly positive reactions more definitely shown by the Kolmer test while the difference between the total number of positive reactions detected was small (6).

Of the sera negative to the Kolmer test 0.25% were positive to the Boerner-Lukens test and 0.04% were positive to the Kline test.

Of the sera negative to the Boerner-Lukens test 0.17% were positive to the Kolmer test and 0.08% were positive to the Kline test.

Of the sera positive to both complement fixation tests 0.09% were negative to the Kline flocculation test.

Considering the positive reactions as a whole, the Kolmer test detected 1.3% more positive reactions than the Kline test, while the Boerner-Lukens test detected 1.9% more positive reactions than the Kline test and 0.6% more than the Kolmer test.

We do not believe that from differences such as these any far reaching or conclusive inferences may be drawn concerning the relative sensitivity of the methods in question.

For, as the experience of serologists in general has decisively demonstrated, it is practically impossible to obtain complete and entire agreement between any two serologic procedures simultaneously applied to any extensive series.

This, it is rather generally believed, results more from inherent variations in the affinity of the serum lipids for the lipids in various antigen suspensions than from any inherent or marked variation in the sensitivity of the methods in question which is only to be inferred when such differences in the reactions obtained are both numerous and marked.

Our purpose in this study was not to determine differences in sensitivity but rather to ascertain if the Boerner-Lukens method compared with two methods shown by our own experience, as well as by the general experience of many others, to possess an acceptable degree of delicacy and sensitivity.

One of the difficulties apt to be encountered when specimens are received from various sources, under various conditions and in varying stages of preservation, is the occurrence of anticomplementary reactions. In our experience with the Kolmer test the incidence of such reactions has consistently been less than 1% and it is of some interest that in this series the number of anticomplementary sera (11) was the same for both complement fixation procedures.

**Summary.** From this study we believe that, in addition to being economical in reagents, time and labor, the Boerner-Lukens modification of the complement-fixation test is shown to possess a degree of sensitivity and delicacy warranting its inclusion among the procedures acceptable for general use in the serologic study of syphilis.

We believe, further, that Department of Health Laboratories

which hitherto may have omitted complement fixation tests for syphilis for the principal reason of the time and labor expended will find the Boerner-Lukens technique, especially in its qualitative form, well suited to their needs.

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### ACUTE LYMPHOCYTIC CHORIOMENINGITIS.

#### REPORT OF THREE CASES WITH HISTOPATHOLOGIC FINDINGS.

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IN 1931 Gibbens<sup>4</sup> directed the attention of the medical world to a group of unusual and little understood infections of the central nervous system, especially one described under various names, but which in the absence of definite knowledge he preferred to call acute aseptic meningitis. Although described by Wallgren in 1925 as "a new infectious disease of the central nervous system," Gibbens states that as early as 1910 14 cases were published in Paris under various titles such as "syndrome meningé avec lymphocytic rachidienne d'origine indéterminée" (Laubry and Foy) and the like.

According to Collis,<sup>2</sup> since the important communication of Wallgren a large number of cases presenting a similar syndrome have been described in various countries of Europe and America. Hughes<sup>5</sup> reported 2 cases in the Malayas which he claimed to be representative of half dozen other cases, Asiatic as well as European. In his opinion the incidence in the Malayas is comparable to that of European countries; all races being equally affected on the peninsula.

The syndrome is characterized by its acute onset, with definite meningeal signs, including changes in the cerebrospinal fluid, such as increased fluid and pleocytosis (predominantly lymphocytes), coupled with little or no change in the fluid sugar and protein; absence of known pyogenic infections, especially otitis media, sinusitis, and so on; and a usually short course and favorable termination.

The relatively benign course as well as the failure to demonstrate the etiologic agent, besides causing considerable confusion in the nomenclature, has hitherto caused these cases to be looked upon rather lightly. In 1935, Collis declared that these cases should no longer be regarded as medical curiosities, and advanced the proba-



bility that the etiologic agent may have been a virus until then undiscovered. This question of a virus etiology has received a great deal of consideration; but is now generally considered satisfactorily answered in favor of the virus isolated by Armstrong and Lillie in 1934,<sup>1</sup> and later by other experimenters in this country as well as in Europe. It has been cultivated on the chorio-allantoic membrane of the chick embryo. Its recovery from all tissues and organs of experimental animals points to it as a systemic rather than entirely a local infecting agent.

The diagnosis is made chiefly on the clinical findings, and clinched by serologic evidences of the presence of the Armstrong virus in the spinal fluid. Tuberculous meningitis is ruled out chiefly by the absence of the tubercle bacillus, and the relatively undisturbed sugar and protein content of the cerebrospinal fluid; also the relatively benign course and favorable termination. Non-paralytic poliomyelitis, according to Lucchesi,<sup>6</sup> is clinically indistinguishable from an uncomplicated syndrome of lymphocytic choriomeningitis. The same may be said of mild cases of encephalitis, except, perhaps, where epidemics of these more serious conditions exist. In case of doubt, however, the virus (where possible) may be identified by its immunologic characteristics.

The literature dealing with complications and sequelæ has been reviewed by Skogland and Barker.<sup>9</sup> Mention has been made of residual involvement of the central nervous system, including periodic headaches, dizziness, strabismus, fatigue, forgetfulness, personality changes, Parkinsonism, chronic arachnoiditis with spastic paraplegia, and chronic meningoencephalitis.

With regard to histologic changes, most of our information has been obtained from experiments on mice and monkeys. Recently a few human cases have been reported with necropsy findings. In 1934 Gallet<sup>3</sup> published his paper entitled "*Méningite à liquide clair et à lymphocytes, comateuse, d'emblée mortelle, chez une ancienne méningite lymphocytaire.*" Unfortunately, no histologic studies were made and the diagnosis was never confirmed. In 1934, Riggs<sup>8</sup> presented a case to the Philadelphia Neurological Society in which meningoencephalitis was present. Viets and Warren<sup>10</sup> were apparently the first to report a fatal case with detailed studies of histologic changes. According to their findings both meningitis and encephalitis were present. The characteristic changes included lymphocytic infiltrations, mostly perivascular; also petechial hemorrhages, glial nodules and large swollen ganglion cells filled with inclusion bodies and pigmented granules. The reaction was most marked in the regions of the midbrain and pons. In 1939, Machella, Weinberger and Lippincott<sup>7</sup> reported another fatal case with autopsy findings, the essential histologic changes including marked thickening of the meninges due to connective tissue proliferation with obliteration of the subarachnoid spaces. The meninges were infiltrated with

lymphocytes, red blood cells, and macrophages. The ependyma of the entire ventricular system was denuded and fragmented, the walls studded with ependymal granulations, and a narrow subependymal zone the site of intense inflammatory reaction. The choroid plexus was partly necrotic and heavily infiltrated with inflammatory exudate. In the floor of the fourth ventricle the process was sufficiently severe to cause softening involving especially the acoustic tubercle and right medial vestibular nucleus. The authors considered unusual the fact that while the meninges, ventricular walls, and choroid plexuses showed intense inflammatory reaction, the remainder of the brain substance was essentially normal.

It is obvious to those acquainted with the present literature that owing to the scarcity of necropsy material the extent and character of the histologic changes in acute lymphocytic choriomeningitis are in need of further clarification. Cases coming to necropsy with the clinical diagnosis of lymphocytic choriomeningitis therefore assume corresponding importance. Accordingly, 3 such cases are here reported.

**Case Reports.** CASE 1.—C. C., a 72-year-old white male, was brought to the Colorado General Hospital on September 18, 1939 by his niece, with the complaint that 3 days before he developed a sore, painful back. He complained a great deal, but continued to work until the next day when he became irrational, following an attack of severe headache. The day before admission he developed peculiar muscular movements, such as clutching at the bed clothes and bicycle riding, and finally had to be restrained. His past history showed that on August 30, 1936, he was previously hospitalized because his prostate was enlarged and painful, but he was discharged on September 18, 1936, improved.

Upon admission the temperature was 102.4° F., pulse 100, and respiration 25. The blood pressure was 152/85.

When examined, he was lying quietly in bed, apparently awake, but unresponsive. He gave the impression of being quite ill. The skin was hot and dry, and gave evidence of much weight loss. His constricted pupils reacted slowly to light. The retinal arteries showed marked crossing signs and silver-wire effects. Ears, nose and mouth showed nothing of particular interest. The neck was held rigid and could not be flexed; lateral movements not restricted. The chest was apparently in fairly good condition. On previous hospitalization, August 30, 1936, the electrocardiogram was normal. Abdomen and external genitalia were essentially negative, but the prostate was approximately three times the normal size. It was smooth, firm and unfixed. Reflexes were hyperactive. There were present a right Babinski, bilateral Kernig and Brudzinski signs.

The clinical impressions were: lymphocytic choriomeningitis, generalized arteriosclerosis, and prostatic hypertrophy. Laboratory findings: The urine showed specific gravity of 1.016, was otherwise negative. Blood: hemoglobin, 15.5; red blood cells, 5,850,000; white blood cells, 14,000; hemogram normal. Sedimentation rate was 4% in  $\frac{1}{2}$  hour; 6% in 1 hour. The Wassermann reaction was negative. Blood sugar was 94 mg. per 100 cc.; non-protein nitrogen, 84 mg.; urea, 63; and creatinine, 2.5 mg. per 100 cc. Spinal fluid findings on September 20, 1939, were: pressure,

300 mm. of water; cells, 100 (lymphocytes and a few red cells); protein, 70mg.; sugar, 53 mg.; Wassermann, negative; colloidal gold curve, 000110000.

The patient was given 3000 cc. of 10% glucose in Ringer's solution, covered by 20 units of old insulin. This was done repeatedly in efforts to restore fluids, supply nutrition and overcome the consequences of dehydration. However, the hospital course was predominantly downhill. Consciousness was never regained. His temperature fell to 98.4° F. on the third day, but soon climbed back to 103° F. It fell again on the fifth day, but rose steadily back to 104° F., when he expired. Diagnosis: acute lymphocytic choriomeningitis.

**Autopsy findings:** The brain weighed 1475 gm. after embalming. The leptomeninges were slightly thickened, but glistening; no exudate noted. Vessels on the base were greatly thickened, dilated, and showed many yellowish plaques and partly calcified areas. On section, the lateral ventricles were found to be widely dilated. Structures of the gray and white matter appeared to be without hyperemia, softenings or hemorrhages. In the lower right half of the midsection of the pons a couple of old cysts, probably due to softening, were seen, the only ones noted.

The histologic changes were quite impressive. The leptomeninges showed patchy lymphocytic infiltrations, sometimes perivenous, and generally of moderate degree. This was more pronounced along the brain-stem region, both in the arachnoid spaces and in the meshes of the pia. In all regions of the brain, however, some areas appeared to have been spared. Incidentally, the infiltration as a rule failed to overlap the adjacent gray matter. An unusual amount of melanotic pigment was found to be present in the basal meninges. A very moderate encephalitis was observed in extra-cortical regions, including the basal ganglia, substantia nigra, pons, olivary nucleus, and cerebellum. This was characterized by lymphocytic infiltrations (chiefly perivenous), noticeably absent from the cortex and white matter, and, incidentally, from the plexuses as well. Glia stars appeared mostly in the cerebellum, olivary nucleus, substantia nigra, and to a less degree in the cortex and white matter. Shrub-like proliferations also were observed in the cerebellum. The substantia nigra, while generally well preserved, exhibited foci of black pigment scattered about the nerve cells or ingested by glial phagocytes. In addition to the meningitis and encephalitis there was present some arterio- and arteriolosclerosis; but areas of softening were lacking except for those in the pons already mentioned. Diagnosis: lymphocytic choriomeningitis with moderate encephalitis. In other organs the main findings were: confluent bronchopneumonia in lower half of both lungs, hypertrophy of the heart, moderate nephrosclerosis, hypertrophy of the prostate, and generalized arteriosclerosis.

**CASE 2.**—C. J., a 67-year-old white male, was admitted to the Colorado General Hospital on August 21, 1938. Two weeks before, he had complained of numbness of both hands, occasionally severe headaches, and fever. Since that time there have been generalized aches and pains about the body with stiffness ascending to the neck. He was comatose when admitted, and there was rectal incontinence which had begun two days before. Temperature was 103.4° F.; pulse 96; and respiration rapid and labored. Past history was of little interest. Six years ago there was an attack of "nervous indigestion," followed shortly by pneumonia. Four years previous to this, a nervous breakdown was said to have resulted from financial stress. Examination revealed alopecia, a hot dry skin, slight neck rigidity, and limited chest expansion. The heart rate was rapid, but the rhythm regular. An apical systolic murmur and an accentuated pulmonary second sound were present. The rectal sphincter was relaxed; the prostate was apparently enlarged to palpation. There was moderate rigidity of all extremities. Peripheral vessels were hard and beaded; blood

pressure, 184/148. Deep reflexes were apparently increased; superficial reflexes diminished.

Laboratory findings were as follows: Urine, specific gravity 1.016, albumin 2, hyaline casts 4, coarse granular casts 2. Blood: hemoglobin, 15.2; red blood cells, 4,800,000; white blood cells, 10,000 (80% neutrophils); sugar, 134 mg.; non-protein nitrogen, 60 mg., and creatinine, 2 mg. per 100 cc. Spinal fluid: pressure normal, cells 40 (mostly lymphocytes), sugar 66 mg. and protein 41 mg. Wassermann reaction negative; colloidal gold curve 0001221000; no bacteria.

The temperature curve was predominantly febrile, with daily spikes. On August 27, 1938, his condition was obviously critical; temperature was 103° F.; respiration of the Cheyne-Stokes type. Oxygen was administered, but he expired on August 29, 1938, at 12.45 noon.

*Autopsy:* The gross findings were mainly as follows: stretching of the dura and slight thickening of the leptomeninges with globular thickenings of the subarachnoid membrane by accumulations of cerebrospinal fluid. The brain itself weighed 1140 gm. The cortex was atrophic, and there were numerous foci of partly cystic softenings of different sizes in right thalamus, left internal capsule, and pons. There were remainders of small hemorrhages in the left dentate nucleus and a globular fresh hemorrhage in the left frontal lobe. The ventricles were slightly dilated. The basal vessels were sclerosed, partially thickened, and contained many yellowish plaques in the intima. The microscopic findings were essentially those of a meningitis with encephalitis, the latter characterized by marked lymphocytic infiltrations around small vessels located chiefly in the substantia nigra and pons; predominantly in the locus caeruleus. Ganglion cells everywhere showed slight evidences of fresh degeneration, such as swelling, vacuolation and loss of Nissl substance. The corpus callosum too was involved in the form of dilated vessels with petechial hemorrhages, and perivascular lymphocytic infiltrations. The glial reaction was essentially in the form of scattered nodular proliferations. The leptomeninges showed patchy lymphocytic infiltrations, in the subarachnoid spaces as well as in the meshes of the pia. The plexuses were thickened by fibrous proliferations and contained many corpora amylacea and scavenger cells filled with fat and pigment. All changes were predominant in the pons and mid-brain regions. The arteriosclerotic changes were apparently incidental and not directly connected with the inflammatory process. Diagnosis: subacute lymphocytic choriomeningitis with encephalitis, arteriosclerosis.

CASE 3.—A. S., a 79-year-old white female, was brought to necropsy with the clinical diagnosis of acute lymphocytic choriomeningitis. She had not been previously hospitalized.

Necropsy findings: The brain was found to be grossly atrophic. The basal vessels were sclerosed; the leptomeninges dull and thick. The white matter was decidedly pale. In contrast, however, the pons was slightly hyperemic. The histologic changes in the meninges were chiefly in the form of patchy lymphocytic infiltrations and moderate fibrosis. The lymphocytes were located predominantly in the meshes of the pia. Although these changes were most marked in the regions of the brain stem, the cortical furrows were well represented. Changes in the brain parenchyma were observed chiefly in the substantia nigra and locus caeruleus, characterized by perivascular lymphocytic infiltrations, mostly of the smaller vessels, with additional destruction of some few ganglion cells and focal glial proliferation. In other brain regions encephalitic changes were scarcely noted, whereas moderate degrees of senile involution were prevalent. Other organs: the most important findings here were bronchiectasis, nephrosclerosis, and generalized arteriosclerosis.

**Discussion.** Despite the fact that no attempt was made to identify the virus of Armstrong in any of the cases here presented, the clinical course and histologic brain changes undoubtedly justified the clinical diagnosis of acute lymphocytic choriomeningitis. Furthermore, as far as can be ascertained, there were no epidemics of poliomyelitis or encephalitis concurrent at the time that these cases were seen, absence of which is considered presumptive evidence in favor of the more benign condition. It may be of some interest to note also that of the few cases coming to necropsy, only in one instance did the histologic studies show uncomplicated involvement of the membrane structures (Machella and coworkers); a finding which was admittedly unexpected by the authors themselves. The presence of complicating encephalitis in the present cases is in agreement with the findings of other authors, especially Viets and Warren, who consider mild encephalitis an important part of the histologic picture. At the present time it is not definitely known whether the encephalitis precedes or follows the meningeal reaction. The pathway of infection is also open to further investigation.

The question of a close relationship between such virus infections as epidemic encephalitis, poliomyelitis and acute lymphocytic choriomeningitis has been the subject of much discussion. The prevalence of similarity in clinical as well as pathologic findings has led to the belief that there should be more than mere coincidence attached to these findings.

Although lymphocytic choriomeningitis is considered a disease of early life, middle and old age are not exempt. Of the few cases reported with autopsy findings, one (Machella and coworkers) was 14 years old, and another (Viets and Warren) was 20 years old. In the present series, ages ranged from 67 to 79. No doubt in the aged the syndrome of lymphocytic choriomeningitis may follow a somewhat different course from that seen in the young. Whether or not this be the case, it is reasonable to suppose that lowered vitality as well as the presence of intercurrent infection in the aged are factors which should affect the course in a manner which is most unfavorable. This report therefore can hardly affect the question of benignity in connection with lymphocytic choriomeningitis. The findings, however, are in agreement with those of other authors (Viets and Warren): namely, meningitis, characterized by lymphocytic infiltrations chiefly in the basal leptomeninges, and mild encephalitis in the extracortical regions.

The character of the meningeal reaction deserves some mention in this discussion. The patchy distribution and areas of predilection were in conformity with no other known type of meningeal infection. On the other hand, the intracerebral infiltrations closely resembled in character and distribution changes due to epidemic encephalitis. The predominant perivenous nature of the infiltrations also agrees

with that seen in other virus infections, such as in postmorbilious encephalitis, the significance of which is not clearly understood.

In conclusion, it should be emphasized that the senile changes, such as cortical atrophy, and the arteriosclerotic changes were incidental and quite independent of the inflammatory changes due to the lymphocytic reaction.

**Summary.** Three cases clinically diagnosed as acute lymphocytic choriomeningitis are reported with necropsy findings. In all 3 cases the histologic brain changes were essentially of an acute or subacute meningeal reaction with concomitant encephalitis.

The meningitis was characterized by patchy infiltrations (lymphocytic) of the leptomeninges, most marked in the neighborhood of the midbrain and pons. The encephalitic process was in all cases of moderate intensity, and in distribution corresponded closely with predilection centers of epidemic encephalitis.

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### CERTAIN FACTORS GOVERNING THE INCIDENCE OF CEREBRO-VASCULAR CRISES

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AN interest in the relationship between cardiac and intra-cranial lesions was aroused during a survey of the incidence of cerebrovascular crises in association with coronary artery occlusion.<sup>1</sup> Protocols of 1000 consecutive autopsies performed at this hospital were analyzed and the clinical records studied to determine any particular factors which might govern the occurrence of cerebrovascular accidents.

In this series the brain was examined in 138 instances. Autopsy in 29 other cases showing definite clinical evidence of cerebral lesions did not include brain examination; these are included as "cerebrovascular lesions, type undetermined," thereby establishing a more nearly true cross-section of the group. As the great majority of lesions are related to the vascular system (Table 1), this group was selected for consideration in its relation to heart disease, hypertension, arrhythmia and syphilis, as well as age, sex and race.

TABLE 1.—CHIEF FINDING AT AUTOPSY.

	No. of cases.	Per cent of the total examined.
Cerebral thrombosis . . . . .	77	55.8
Cerebral hemorrhage . . . . .	25	18.1
Thrombosis and hemorrhage . . . . .	4	2.9
Embolism . . . . .	1	0.7
	— 107	
Cerebral thrombosis and myelomalacia of cord . . . . .	1	0.7
Subdural hemorrhage . . . . .	3	2.1
Subarachnoid hemorrhage . . . . .	1	0.7
Extradural hemorrhage . . . . .	1	0.7
Multiple sclerosis and old hemorrhage . . . . .	1	0.7
Meningo-vascular syphilis . . . . .	1	0.7
Marked cerebral arteriosclerosis . . . . .	4	2.9
Old cortical scars . . . . .	2	1.4
Edema and congestion . . . . .	3	2.1
Meningitis (2 miliary abscess) . . . . .	5	3.6
Abscess . . . . .	2	1.4
Tuberculoma . . . . .	2	1.4
Glioma . . . . .	2	1.4
Metastatic carcinoma . . . . .	1	0.7
Fibroblastoma . . . . .	1	0.7
Cerebral atrophy (idiot) . . . . .	1	0.7
	— 31	
Cerebral lesion—type undetermined . . . . .	29	
Total . . . . .	167	

It should be pointed out that, in the following discussion, the term "hypertensive heart disease" is restricted to those cases with hyperpiesis (elevation of systolic and diastolic pressure above 140 and 90 respectively), cardiac enlargement, clinical signs of heart disease without coronary sclerosis of note or myofibrosis; this group was composed chiefly of relatively younger individuals suffering with "essential" or malignant hypertension, or renal disease. "Arteriosclerotic heart disease" includes individuals with or without hypertension in whom the chief pathologic finding is coronary sclerosis and fibrosis of the myocardium, excluding cases of cardiovascular syphilis with focal scarring of the heart muscle.

*Heart Disease.* In the 343 cases of heart disease (Table 2), 116 (33.8%) were complicated by a cerebral lesion, the majority having hemorrhage and thrombosis, whereas the incidence of cerebral lesions in the entire group of 1000 cases was 16.7%. The tabulation indicates that the percentage of cerebral complications was about the same in hypertensive, arteriosclerotic, coronary thrombotic and syphilitic heart disease. The incidence in rheumatic heart disease and acute bacterial endocarditis was less, while subacute bacterial endocarditis and congenital heart disease were represented by too few cases to be of significance. Thus far, then, one may conclude that heart disease in general is a major factor in the occurrence of cerebro-vascular lesions.

*Hypertension per se.* Hypertension was noted in 21.6% of the entire group, and 52% of cardiac cases and 74.2% of individuals

with cerebral accidents were hypertensive (Table 3). A comparison of Tables 2 and 3 indicates that the types of heart disease which are more apt to be complicated by a cerebral lesion are those usually associated with hypertension. As it appears that hypertension is observed twice as frequently in cardiac patients, and cerebro-vascular accidents occur more than twice as commonly in association with cardiac disease, it is reasonable to believe that the hypertension *per se*, rather than the cardio-vascular disease proper (apart from embolic phenomena), is responsible for the cerebral lesions.

TABLE 2.—INCIDENCE AND TYPES OF CEREBRAL LESIONS IN EACH TYPE OF HEART DISEASE.

Heart disease (total No. 343).		Associated cerebral lesions.									
Type.	Number.	No. with cerebral lesion.	Per cent with cerebral lesion.	Cerebral thrombosis.	Cerebral hemorrhage.	Hemorrhage and thrombosis.	Embolism.	Miliary abscess.	Abscess.	Cortical scar.	Type undetermined.
Rheumatic . . . . .	32	7	21.8	3	..	..	1	1	..	..	2
Cardiovascular syphilis . . . . .	52	16	30.7	9	3	..	..	1	..	..	3
Subacute bacterial endocarditis . . . . .	3	2	66.6	..	..	..	1	..	..	..	1
Acute bacterial endocarditis . . . . .	17	2	11.8	..	..	..	..	2	..	..	..
Hypertensive . . . . .	39	12	33.3	8	3	..	..	..	1	..	..
Arteriosclerotic . . . . .	155	62	40.0	31	7	2	..	..	..	2	20
Coronary thrombosis . . . . .	44	15	34.0	11	..	1	..	..	..	..	3
Congenital . . . . .	1	0	0.0								

An attempt to determine the frequency of acute cerebro-vascular accidents following the use of vasodilators in hypertensive individuals was unsuccessful, due to lack of uniformity in certain of the clinical records.

TABLE 3.—INCIDENCE OF HYPERTENSION IN CASES WITH CEREBRAL VASCULAR LESIONS.

Type of cases.	No.	No. with hypertension.	Hypertensives with cerebral complication.
Rheumatic heart disease . . . .	32	7— 21.8%	7—100.0%
Cardiovascular syphilis . . . .	52	17— 32.7%	16— 94.1%
Subacute bacterial endocarditis . .	3	0— 0.0%	0— 0.0%
Acute bacterial endocarditis . . .	17	4— 23.4%	2— 50.0%
Hypertensive heart disease . . .	39	39—100.0%	12— 30.7%
Arteriosclerotic heart disease . .	155	94— 60.7%	62— 66.0%
Coronary thrombosis . . . . .	44	19— 43.1%	15— 78.9%
Congenital heart disease . . . .	1	0— 0.0%	0— 0.0%
	343	180— 52.0%	114— 63.3%
Miscellaneous . . . . .	657	36— 5.4%	10— 27.7%
Entire group . . . . .	1000	216— 21.6%	124 (74.2% of 167)



*Arrhythmias.* Following the suggestion of several authors that arrhythmias may interfere with the cerebral circulation and even be responsible for hemiplegia, this series was analyzed from this standpoint. Of the 1000 cases, 4.3% had auricular fibrillation, while 3.5% of those with cerebral lesions were fibrillating. No case with auricular fibrillation associated with thrombosis of the left auricle or appendage showed an anatomic lesion of the brain, although the possibility of embolism following dislodgment of such thrombotic material is not questioned. There is no doubt, too, that arrhythmias are capable of producing transient cerebral manifestations, due to circulatory alterations with edema of the brain, sometimes of sufficient degree to contribute to or even cause death.

TABLE 4.—RELATION BETWEEN AURICULAR FIBRILLATION AND CEREBRAL LESIONS.

Type of case.	Without auricular fibrillation.		With auricular fibrillation.	
	Number.	No. with cerebral lesion.	Number.	No. with cerebral lesion.
General group . . . . .	957	163—17.0%	43	6—14.0%
Rheumatic heart disease . . . .	21	7—33.3%	9	2—20.0%
Cardiovascular syphilis . . . . .	52	16—30.7%	0	0—0.0%
Subacute bacterial endocarditis . .	3	2—66.6%	0	0—0.0%
Acute bacterial endocarditis . . .	16	2—12.4%	1	0—0.0%
Hypertensive heart disease . . .	36	13—36.1%	3	0—0.0%
Arteriosclerotic heart disease . .	131	62—47.3%	24	3—12.4%
Coronary thrombosis . . . . .	38	15—39.4%	6	1—16.0%
Congenital heart disease . . . . .	1	0—0.0%	0	0—0.0%

TABLE 5.—RELATION BETWEEN SYPHILIS AND CEREBRAL LESIONS.

Type of case.	The Wassermann and percentage with cerebral lesion.			
	Wassermann positive.	Wassermann negative.	No Wassermann history negative.	No Wassermann history positive.
Entire 1000 . . . . .	79—13.9%	445—21.5%	27—14.7%	449—14.6%
Rheumatic heart disease . . . . .	1—0.0%	12—16.6%	1—0.0%	16—17.5%
Cardiovascular syphilis . . . . .	22—36.3%	5—0.0%	4—25.0%	18—22.0%
Subacute bacterial endocarditis . .	0—0.0%	1—100.0%	0—0.0%	1—0.0%
Acute bacterial endocarditis . . .	2—0.0%	4—25.0%	0—0.0%	11—9.0%
Hypertensive heart disease . . . .	2—0.0%	27—33.3%	0—0.0%	10—40.0%
Arteriosclerotic heart disease . . .	6—16.6%	81—32.0%	0—0.0%	50—30.0%
Coronary thrombosis . . . . .	3—0.0%	24—29.0%	0—0.0%	19—26.3%
Congenital heart disease . . . . .	0—0.0%	0—0.0%	0—0.0%	1—0.0%
Cases with cerebral lesions	11	96	4	66

*Syphilis.* Serologic examinations for syphilis in 524 of the cases gave 79 positive and 445 negative results; 27 untested cases volunteered a positive history of syphilis. The incidence of cerebral lesions, in the presumably syphilitic individuals, was lower than in the remaining subjects, although fairly high (30.7%) in those with actual cardiovascular syphilis. It is difficult, however, to evaluate the presence of this disease in the group because of unreliable histories, certain numbers of falsely negative tests, and a scattering of

individuals Wassermann-negative after treatment. In a general way, though, it appears that syphilis is not a very important factor in the etiology of cerebro-vascular accidents.

*Age.* That age is an important factor is shown by the gradual, progressive increase in the incidence of cerebro-vascular lesions with advancing years (Table 6), the apparent fall beyond 80 being due to the relatively few cases studied. This is naturally the case with progressive sclerosis in the cerebro-vascular tree, often complicated by an hypertensive state. Cerebral lesions occur with greater frequency in the lower age groups with rheumatic heart disease; other types of heart disease are more apt to be thus complicated between the ages of 40 and 59 years.

TABLE 6.—INCIDENCE OF CEREBRAL LESIONS AT DIFFERENT AGES.

Type of case.	Age group and percentage with cerebral lesion.				
	Below 20 years.	20 to 39 years.	40 to 59 years.	60 to 79 years.	80 and above.
Entire 1000 . . . . .	88— 5.6%	200— 7.5%	406—12.5%	256—19.9%	50—16%
Rheumatic heart disease . .	6— 33.3%	11—18.0%	9—11.0%	6—33.0%	
Cardiovascular syphilis . .	....	6— 0.0%	32—34.0%	14—35.0%	
Subacute bacterial endocarditis	1—100.0%	2—50.0%			
Acute bacterial endocarditis .	....	10—10.0%	5—20.0%	2— 0.0%	
Hypertensive heart disease .	....	7—42.8%	28—32.0%	4—25.0%	
Arteriosclerotic heart disease	....		49—47.0%	99—33.0%	7—85%
Coronary thrombosis . . . .		5—60.0%	23—30.0%	15—33.3%	
Congenital heart disease . .	1— 0.0%				
Cases with cerebral lesions .	5	17	68	67	10

TABLE 7.—COMPARISON OF THE INCIDENCE OF CEREBRAL LESIONS IN THE TWO SEXES AND IN THE WHITE AND COLORED RACES.

Type of case.	Sex and color and percentage with cerebral lesion.			
	Female.	Male.	White.	Colored.
Entire 1000 . . . . .	433—27.2%	567— 8.6%	626—19.1%	374— 8.8%
Rheumatic heart disease . .	20—30.7%	12— 0.0%	23—21.7%	9—22.2%
Cardiovascular syphilis . .	11—13.4%	41—29.2%	21—26.2%	31—29.9%
Subacute bacterial endocarditis	0— 0.0%	3—66.6%	3—66.6%	0— 0.0%
Acute bacterial endocarditis .	10—20.0%	7— 0.0%	12— 8.9%	5—20.0%
Hypertensive heart disease .	24—45.8%	15— 6.6%	21—42.8%	18—22.0%
Arteriosclerotic heart disease	77—45.4%	78—26.9%	117—32.4%	38—54.5%
Coronary thrombosis . . . .	18—22.2%	26—42.3%	26—42.3%	18—22.2%
Congenital heart disease . .	1— ...	0— ...	1— 0.0%	0— ...
Cases with cerebral lesions	118	49	120	47

*Sex and Race.* There were 567 males and 433 females in the series. Cerebro-vascular lesions occurred in 8.6% of males as opposed

to 27.2% of females, the 1 : 3 ratio in a thousand cases being regarded as significant. Whites outnumbered negroes 626 to 374, with cerebral accidents occurring in 19.1 and 12.6% respectively. It is interesting to note that the preponderance of cerebral lesions associated with cardiovascular syphilis appeared in males and that all females with cardiovascular syphilis were colored. Coronary thrombosis accompanied by cerebral lesions was more frequent in males, particularly whites between 40 and 59 years.

**Summary.** The clinical and autopsy records of 1000 consecutive, unselected cases were studied to determine any correlation between cerebro-vascular lesions and heart disease, hypertension, arrhythmia, syphilis, age, sex and race, the following conclusions being drawn:

1. Hypertension is probably the most important single etiologic factor in cerebro-vascular crises.

2. Heart disease in general is a major etiologic agent.

3. There is a gradual, progressive increase in incidence with advancing age, excepting the younger group associated with rheumatic heart disease.

4. Cerebro-vascular lesions occur 3 times as frequently in females as in males and nearly twice as often in whites as in negroes.

5. Syphilis *per se* has little influence; the percentage found with cardiovascular syphilis approaches that of heart disease in general.

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## THE EFFECT OF PARTIAL HEPATECTOMY ON THE ACTION OF CERTAIN BARBITURATES AND A PHENYLUREA DERIVATIVE.

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CHLOROFORM and carbon tetrachloride are liver poisons commonly used to produce experimental hepatic damage. These substances have found considerable use in studying the protective function of the liver against certain noxious agents.

Pratt and his coworkers<sup>13</sup> noted that experimental liver injury prolonged the action of certain of the hypnotic drugs. They found a decreased tolerance to pentobarbital sodium in dogs whose livers had previously been injured by chloroform. Pratt<sup>12</sup> later found a

close correlation between the functional activity of the liver as determined by the bromsulfalein test and the duration of action of pentobarbital sodium. Carbon tetrachloride was used to produce hepatic injury. The action of barbital sodium, however, was not increased when administered to a dog with a damaged liver. He concluded that the short-acting pentobarbital sodium was rapidly destroyed by the liver, whereas barbital sodium was more stable and was not detoxified. This was supported by the fact that barbital sodium is largely excreted unchanged in the urine.

Cameron and de Saram<sup>3</sup> found that the duration of anesthesia produced by pentobarbital sodium and evipan was more than doubled following liver injury produced by carbon tetrachloride in rats. Acute liver damage did not significantly affect the action of barbital sodium or phenobarbital.

Neither of the hepatotoxins, chloroform or carbon tetrachloride, which were used in the foregoing studies, is specific in its action since, in addition to producing hepatic necrosis, they result in a certain amount of generalized tissue injury.<sup>2,5,9</sup> Koppányi<sup>9</sup> had this in mind when he advanced a hypothesis to explain the increased potency exhibited by certain barbiturates in the presence of liver damage. He suggested that the hepatotoxin, chloroform, injured the central nervous system so that the nerve cells became more susceptible to the barbiturates. He further suggested that the general depression in cellular metabolism resulting from the hepatotoxin might be a factor in increasing the potency of the barbiturates following chemical injury of the liver. A method which would eliminate a constant amount of functioning hepatic tissue without introducing other unmeasurable factors would be desirable. Such a method is found in partial hepatectomy.

One of us (Higgins) and Anderson<sup>7</sup> found that restoration of the liver following partial hepatectomy in the rat began toward the end of the first 24 hours. The remnant more than doubled itself in 72 hours and by 10 to 14 days the ratio of liver weight to body weight was restored to normal.

It was thought that if the liver actually did protect against the action of certain drugs, then removal of a portion of this organ should increase the potency of these substances. Similarly, restoration of the liver should be accompanied by a corresponding decrease in the effects of their action.

In our experiments three drugs of the hypnotic-anesthetic group were tested, namely ethyl-o-ethylphenylurea,\* a hypnotic of low toxicity,<sup>8</sup> pentobarbital sodium (nembutal) and pentothal sodium.† Ethyl-o-ethylphenylurea was administered intraperitoneally to rats in doses of 100 mg. per kg. The barbiturates were given intra-

\* Supplied by Burroughs Wellcome & Co., Inc., through the courtesy of Dr. R. C. Page. Not released for clinical use.

† Supplied through the courtesy of the Abbott Laboratories.

venously,<sup>14</sup> pentobarbital sodium in 1% aqueous solution and pentothal sodium in 2% solution. The doses were 25 and 30 mg. per kg. respectively. The duration of action of these substances was taken as the interval during which the rats would lie quietly on their backs or sides. The rats were tested frequently to make sure that physiologic sleep was not superimposed on the induced sleep.

Over a period of five trials in which ethyl-o-ethylphenylurea was given, the duration of anesthesia averaged 42 minutes in a group of 8 rats (Chart 1). Then partial hepatectomy was carried out. Seventy per cent of the liver was removed by this procedure. Two days later the drug was again administered. At this time the duration of

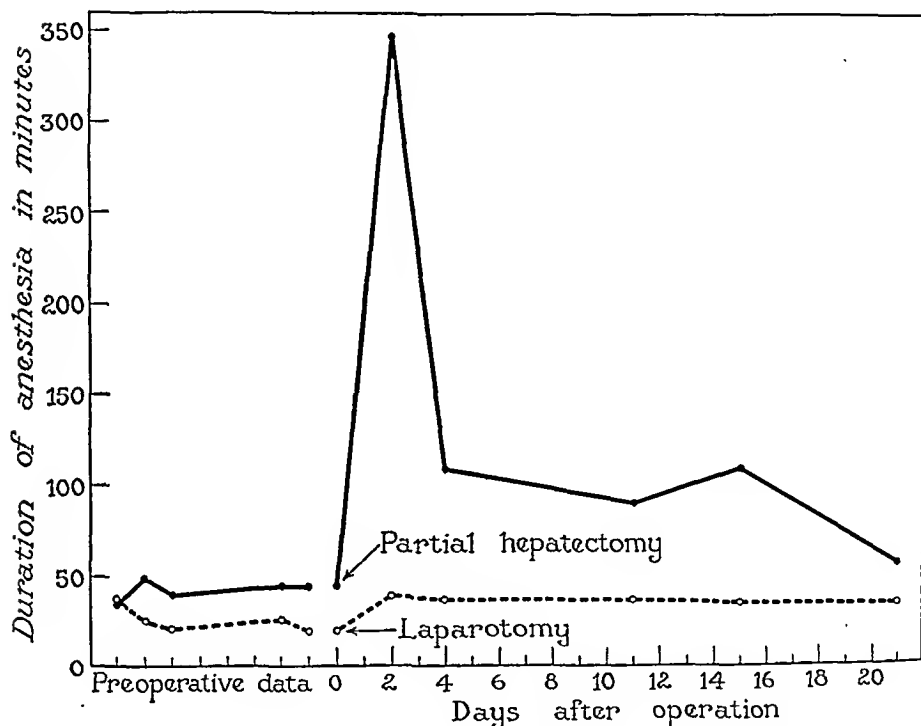


CHART 1.—Effect of partial hepatectomy on the action of ethyl-o-ethylphenylurea.

anesthesia had increased to 347 minutes or about eight times the preoperative level. On the fourth postoperative day when the liver was more than half restored, the duration of anesthesia had decreased to 118 minutes, still about three times the preoperative level. Thereafter it decreased but tended to lag behind the corresponding degree of hepatic restoration.

In the control series the drug was given at corresponding intervals but instead of partial hepatectomy, laparotomy was done. There was only a slight prolongation of anesthesia following laparotomy.

In a series of 7 rats, pentobarbital sodium was given every 2 days for a period of 5 trials. It was noted that for each rat a degree of

tolerance was developed after the first dose,<sup>11</sup> but in the remaining 4 trials the duration of anesthesia remained around  $50 \pm 5$  minutes (Chart 2). On the second day following partial hepatectomy the duration of anesthesia had increased to 212 minutes or four times the preoperative level. Thereafter it decreased in an irregular but definite manner until by the fourteenth postoperative day it was within the preoperative range.

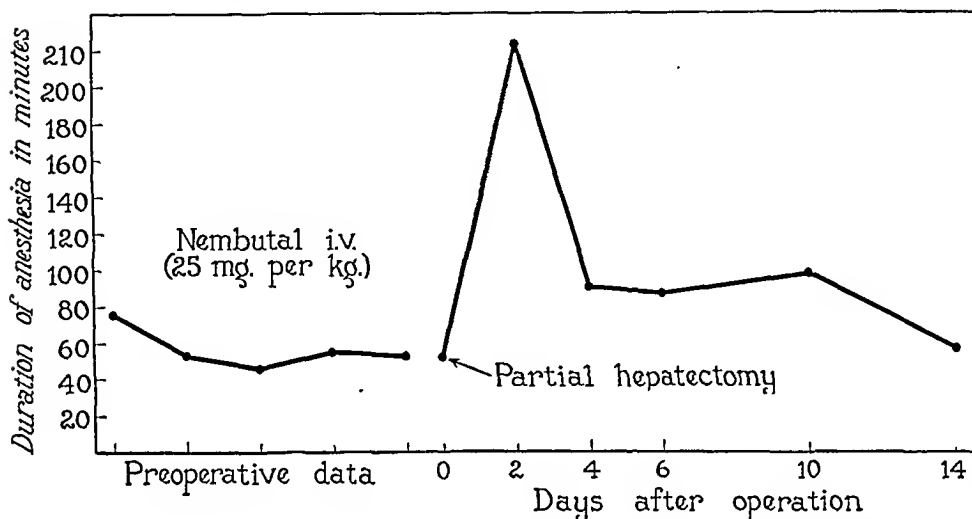


CHART 2.—Effect of partial hepatectomy on the action of pentobarbital sodium.

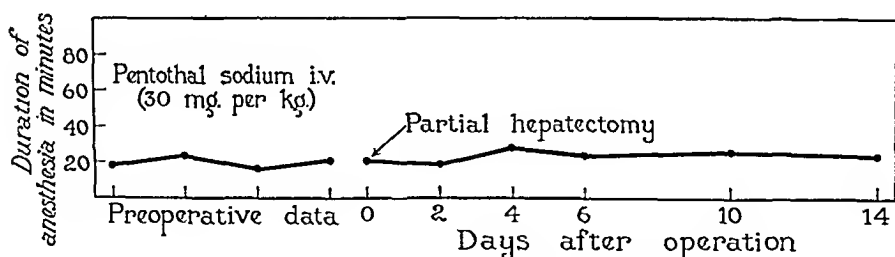


CHART 3.—Effect of partial hepatectomy on the action of pentothal sodium.

The action of pentothal sodium was studied in 9 rats, using the same technique. Partial hepatectomy had no significant effect on its action (Chart 3).

Unilateral nephrectomies were done on 6 rats to serve as controls. This procedure had no effect on the action of either pentobarbital sodium or pentothal sodium.

**Comment.** It has frequently been stated that the short-acting barbiturates are unstable and so are quickly destroyed in the body, presumably by the liver, whereas those of longer action, being more stable, resist detoxication and are largely excreted in the urine.<sup>1,12,14</sup> Pentobarbital sodium is one of these short-acting barbiturates.

The results of this study show that its action is increased by a reduction in the amount of functioning hepatic tissue, thus suggesting destruction by the liver. Pentothal sodium is even more short-acting than pentobarbital sodium and is its sulphur-containing homologue. Thus, it was expected that partial hepatectomy would prolong the action of pentothal sodium even more than that of pentobarbital sodium. This did not occur. Although several writers have attributed its destruction to the liver,<sup>6,10</sup> these data suggest that the liver is little concerned with the destruction of pentothal sodium. Clinical support of this observation is found in Adams' statement that "it has been observed clinically that patients who have hepatic damage appear to require as much of the drug to produce narcosis as do those patients who have no hepatic damage."<sup>4</sup>

As for ethyl-o-ethylphenylurea, this study simply shows that its action is augmented by a reduction in the amount of functioning hepatic tissue.

The method of partial hepatectomy has eliminated both the possibility of induced nerve cell hypersensitivity and generalized tissue injury from the interpretation of results, thus defining more clearly the protective function of the liver.

**Summary and Conclusions.** The duration of anesthesia in rats produced by ethyl-o-ethylphenylurea and pentobarbital sodium was markedly prolonged following partial hepatectomy. This procedure had no effect on the action of pentothal sodium. Unilateral nephrectomy did not prolong the action of either pentobarbital sodium or pentothal sodium. These data suggest that the liver is instrumental in protecting the animal against the action of ethyl-o-ethylphenylurea and pentobarbital sodium but does not protect against the action of pentothal sodium.

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## BOOK REVIEWS AND NOTICES

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OBSTETRICS AND GYNECOLOGY. In two volumes. By the Departmental Staff of The University of Chicago and Other Contributors. Edited by FRED L. ADAIR, M.A., M.D., F.A.C.S., Mary Campau Ryerson Professor and Chairman of the Department of Obstetrics and Gynecology in The University of Chicago; Chief of Service, The Chicago Lying-in Hospital, Chicago. Pp. Vol. 1, 1000; Vol. 2, 1031; illustrations Vol. 1, 359 and 14 plates; Vol. 2, 304 and 10 plates (plates mostly in color). Philadelphia: Lea & Febiger, 1940. Price, \$20.00.

THERE has been an increasing tendency in recent years toward combining obstetrics and gynecology for the purposes of practice, teaching and research. This fact is being recognized more and more by the publication of such combined books as the present ones.

These two volumes take up their subjects in the following order: 1, Basic biologic relationships of the human female. 2, Approach to individual and communal problems. 3, Life cycle of the human female. 4, Normal and abnormal conditions of the non-pregnant and pregnant woman. 5, Normal and abnormal conditions of the parturient woman. 6, Normal and abnormal conditions of the postpartum woman and of the newborn infant. 7, Diseases of the female genitalia. 8, Medical and surgical specialties in relation to obstetrics and gynecology. 9, Obstetric and gynecologic operative procedure.

The authors have devoted more space to obstetrics than to gynecology, in which selection the Reviewer heartily agrees. They present the point of view of their own clinic, rather than give many points of view upon subjects which are still in a state of flux. They purposely have omitted a detailed treatment of many technical matters in order to give more emphasis to principles than practice. Many subjects not heretofore covered in textbooks of gynecology and obstetrics receive careful and interesting treatment. All topics are considered from a very sane and broad point of view. The Reviewer is impressed chiefly by the wide variety of subjects touched upon and the large amount of very interesting material which has been brought together in one set of books. Both volumes make very interesting reading. They would seem to be excellent additions to the library of the general practitioner as well as the specialist. The undergraduate, however, usually demands a short cut to knowledge, which means volumes of small size.

D. M.

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THE MEDICAL CAREER AND OTHER PAPERS. By HARVEY CUSHING. Pp. 302. Boston: Little, Brown & Co., 1940. Price, \$2.50.

THE 16 addresses and biographical sketches that comprise this volume were selected for publication by the author in the summer before his death. As explained by Dr. Fulton in the Preface, it forms a companion volume to *Consecratio Medici*, all but 3 of the collection having appeared since publication of the latter in 1928. The 7 essays are all "occasional," mostly presidential addresses, ranging from advice to Dartmouth students ("The Medical Career"), through consideration of medical societies, schools and libraries to one of the author's own specialty ("Psychiatrists, Neurologists and Neurosurgeons"). Beaumont, the Drs. Welch, Halsted, James Ford



Rhodes, George Derby, Perry Williams Harvey, Haller, Councilman and the Mayo brothers are the subjects of the biographies. Authors of lesser ability might easily be hampered by subject restrictions, in the composition of such essays, necessarily carried out amid the distractions of an active surgical practice. But not so Dr. Cushing! As one should expect from his previous literary efforts, he has woven into his presentations a pleasing combination of practical common sense and humor—now and then with an edge to it—of historical knowledge and shrewd insight into present and probable future trends. The essays disclose an able man of letters and illustrate what may be got from thoughtful and understanding study of medical history.

E. K.

**POISONS. THEIR ISOLATION AND IDENTIFICATION.** By FRANK BAMFORD, B.Sc., Late Director of the Medico-Legal Laboratory, Cairo. With a Foreword by PROF. SYDNEY SMITH, M.D., F.R.C.P., Regius Professor of Forensic Medicine, University of Edinburgh. Pp. 344; 21 illustrations. Philadelphia: The Blakiston Company, 1940. Price, \$4.00.

THIS book can be recommended as a practical laboratory manual for chemists engaged in the detection of poisons. The material, concisely presented, credibly covers the field of Forensic Chemistry. Chapter X contains a qualitative analytical scheme for the identification of the alkaloids and will be especially welcomed by toxicologists.

F. S.

**ARTIFICIAL PNEUMOTHORAX.** Its Practical Application in the Treatment of Pulmonary Tuberculosis. Contributions by Saranac Lake Physicians to the Studies of the Trudeau Foundation. Editorial Committee: E. N. PACKARD, M.D., J. N. HAYES, M.D., and S. F. BLANCHET, M.D. Foreword by E. R. BALDWIN, M.D. Pp. 300; 85 illustrations and 33 tables. Philadelphia: Lea & Febiger, 1940. Price, \$4.00.

SEVENTEEN physicians of the Saranac Lake group have contributed chapters to this compact monograph. Intended as a practical handbook, the volume is simple and comprehensive. The selection of cases, choice of apparatus, technique of operation, and management of treatment are discussed. Detailed consideration is given to the numerous complications of pneumothorax therapy. The place of artificial pneumothorax in the treatment of tuberculosis is sanely evaluated. Those experienced in pneumothorax will find the book relatively elementary. Those gathering their early experience in this form of therapy, on the other hand, will find it very useful as a guide.

H. I.

**THE BRITISH ENCYCLOPÆDIA OF MEDICAL PRACTICE** including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. *Cumulative Supplement, 1939* (pp. 170; 1 illustration); *Surveys and Abstracts, 1939* (pp. 655; 26 illustrations). Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. Publishing Editor, ADAM CLARK, L.M.S.S.A., Sub-Editor, G. FAULKNER, D.Sc. London: Butterworth & Co. (Publishers), Ltd., 1940. Price, \$9.00 per volume.

THIS encyclopedia now publishes 2 volumes such as these annually. The large supplementary volume of Surveys and Abstracts for 1939 is chiefly devoted to abstracts of current medical literature arranged alphabetically by subject, with frequent references to the original treatment of the subject in earlier volumes. The subjects, which range from abdominal pain to yellow fever, are not listed separately, though of course all appear

in the index. This section, like similar abstract annuals, is useful in offering the reader a critical selection from the vast amount of published work. The earlier portion of the book contains "critical surveys" of 27 topics, some covering whole specialties, others such items as Q fever and contact lenses, with 2 surveys on drugs.

The smaller Cumulative Supplement, following the same alphabetical method as the former volume, aims to present new and generally accepted medical knowledge, replacing the presentation of the original volume and in turn to be replaced by the volume of the next year. It must be used "in conjunction with the original volumes of the Encyclopedia," and with the Surveys and Abstracts to which frequent reference is made. This seems like a cumbersome method, its only advantage over the loose-leaf systems being that there are no loose leaves to be inserted. E. K.

**DIAGNOSIS AND TREATMENT OF HEAD INJURIES.** By SIDNEY W. GROSS, M.D., F.A.C.S., Attending Neurosurgeon, Beth Israel Hospital; Associate Neurosurgeon, Morrisania City Hospital; Adjunct Neurosurgeon, Mt. Sinai Hospital, etc., and WILLIAM EHRLICH, M.D., Associate Attending Neurosurgeon, Newark Beth Israel Hospital; Neurosurgeon, Barnett Memorial Hospital, Paterson, etc. Introduction by PERCIVAL BAILEY, M.D., PH.D., Professor of Neurology and Neurosurgery, University of Illinois, Chicago. Pp. 275; 94 illustrations. New York: Paul B. Hoeber, Inc., 1940. Price, \$5.00.

THIS is a well-written, close-knit book that supplies adequate information on the diagnosis and treatment of head injuries without introducing controversial or non-essential material. The chapters on anatomy, physiology and pathology of cranial trauma are short and concise but cover all important details. Methods of examination are briefly outlined and their relative values stressed. In discussing the classification of head injuries any lengthy discussion as to the nature of concussion has been wisely avoided. The chapter on treatment is well thought out, the dangers of dehydration and indications for and against lumbar puncture clearly indicated, with emphasis on rest as the best means of handling these cases.

In discussing the management of compound fractures the methods used in handling cases which are complicated by dural tears and a cerebrospinal fluid leak are properly described in greater detail. The clinical picture accompanying extradural and chronic and acute subdural hemorrhage is adequately discussed and the operative treatment, a sub-temporal decompression for extradural, and bilateral trephines or a small bone flap for subdural clots given concisely.

In the chapter on skull fracture involving the sinus greater emphasis might perhaps have been laid on the dangers of irrigating the external canal of an ear through which cerebrospinal fluid is escaping. Meningitis, brain abscess and osteomyelitis together with the treatment of these complications are briefly discussed.

An adequate description of the proper methods of handling gunshot wounds of the head based for the most part on Cushing's technique developed in the first World War is of timely interest. A chapter is devoted to a description of the armamentarium necessary for the surgical procedures demanded by cranial traumatic cases. Finally the sequelæ consequent upon head injury are discussed. It seems unfortunate that emphasis has been placed upon the relationship between cranial trauma and brain tumor, although in discussing the medico-legal aspects of post-traumatic sequelæ this subject could not have been avoided.

This book can be recommended for students and general practitioners especially as giving a straight-forward conservative description of the

methods best established for the treatment of cranial trauma. Incidentally the introduction by Percival Bailey affords an excellent text around which to write a book on this subject as he outlines very clearly the general principles of such management.

The format is good, the type large and pleasing to the eye, the illustrations adequate and pertinent to the context.

F. G.

**THE MARCH OF MEDICINE.** Edited by the Committee on Lectures to the Laity of the New York Academy of Medicine, WILLIAM C. WHITE, Chairman. Pp. 168; 1 illustration. New York: Columbia University Press, 1940. Price, \$2.00.

IN this volume are presented 6 of the 7 lectures comprising the fourth series of the New York Academy of Medicine's lectures to the laity. Dr. Walter C. Alvarez, in "From Folkways to Modern Medicine," illustrates the opposing methods and purposes of the regular and irregular practitioners from the earliest times to the present. Dr. Sanford V. Larkey's "Health in Elizabethan England" contains an immense amount of interesting and thought-provoking information concerning the public health in England's "Golden Age." In "Not So Long Ago," Dr. Cecil K. Drinker warms over entertainingly some of the material that appeared in his book of the same name based on the fascinating diary of his great-great-grandmother, Elizabeth Drinker, of Philadelphia. Dr. Charles Gordon Heyd, in "The Romance of Modern Surgery," by a number of references to early surgical practices points up the boon conferred on humanity by modern discoveries and procedures beginning with ether anaesthesia and "Listerism." Dr. R. G. Hoskins' "Story of Insanity" reviews reforms in the treatment of the insane made possible by gradually more enlightened concepts of the nature of insanity. Dr. Karl A. Menninger rather surprisingly takes before a possibly bewildered public the Case of the Rest of the Medical Profession *vs.* Psychiatry ("The Cinderella of Modern Medicine"), presenting evidence favorable to both sides of the controversy. The volume contains an index.

These rather informal lectures should, as a whole, make pleasant, casual reading for a not-too-critical public, but (with one exception) may possibly leave the more thoughtful layman with a feeling that the constructive values of the opportunity offered have not been fully realized. The full potential value of medical lectures to the laity is as obvious as it is difficult to achieve. One wonders if, in time, such series of lectures will not be as systematically planned and integrated, and composed with as rigorous attention to a desired educational end, as are the best medical courses for students of medicine.

W. McD.

**CHEMOTHERAPY AND SERUM THERAPY OF PNEUMONIA.** By FREDERICK T. LORD, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School; Member of the Board of Consultation, Massachusetts General Hospital, ELLIOTT S. ROBINSON, M.D., Ph.D., Director, Division of Biologic Laboratories, Massachusetts Department of Public Health, and RODERICK HEFFRON, M.D., Medical Association, The Commonwealth Fund; formerly Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health. Pp. 174. New York: The Commonwealth Fund, 1940. Price, \$1.00.

THE authors have presented an accurate, authoritative and comprehensive book on the treatment of pneumonia. This book represents the first complete review of chemotherapy in pneumonia and also brings up to date the use of anti-pneumococci serum. The keynote is found in the first sentence: "Pneumonia is a medical emergency." Throughout this volume the authors

## NEW EDITIONS

stress the importance of an early and accurate diagnosis. Fifty-eight pages are devoted entirely to the use of serum, whereas treatment with sulfapyridine occupies 25 pages. This should in no way be interpreted as indicating the relative importance of the two forms of therapy. Every practicing physician would profit by reading this entire book as it contains practical suggestions pertaining to the intelligent handling of pneumonia patients. H. F.

## NEW BOOKS

*Pathogenic Anaerobic Organisms of the Actinomyces Group.* By DAGNY ERIKSON. (Special Report Series, No. 240 of Medical Research Council.) Pp. 63; illustrated. London: His Majesty's Stationery Office, 1940. Price, 1s. 0d.

*The New International Clinics, Vol. 2 (N.S. 3), 1940.* Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. With 17 Collaborators. Pp. 365; illustrated. Philadelphia: J. B. Lippincott Company, 1940.

The review deals with present concepts of the hypothalamus. *St. Thomas's Hospital Reports. Second Series, Vol. IV.* Editors: PROF. O. L. V. S. DE WESSELOW, MR. C. MAX PAGE, assisted by MR. N. R. BARRET, DR. J. ST. C. ELKINGTON, DR. A. J. WRIGLEY. Pp. 198; illustrated. London: St. Thomas's Hospital, 1939. Price, 10s.

*The Medical Clinics of North America, May, 1940 (Vol. 24, No. 3, New York Number).* Pp. 362; 41 illustrations. Philadelphia: W. B. Saunders Company, 1940.

This New York number contains 29 articles on the usual wide diversity of subjects.

*Complete Guide for the Deafened* (pp. 256) and *Handbook of Hearing Aids* (pp. 156). By A. F. NIEMOELLER, A.B., M.A., B.S. With Forewords by HAROLD HAYS, M.D., F.A.C.S. New York: Harvest House, 1940. Price, \$3.00 each.

*The Varieties of Human Physique.* An Introduction to Constitutional Psychology. By W. H. SHELDON, PH.D., M.D., Harvard University. With the Collaboration of S. S. STEVENS, PH.D., Harvard University, and W. B. TUCKER, M.D., University of Chicago. Pp. 347; 104 illustrations. New York: Harper & Brothers Publishers, 1940. Price, \$4.50.

*A Manual of Otolaryngology, Rhinology and Laryngology.* By HOWARD CHARLES BALLENGER, M.D., F.A.C.S., Assistant Professor of Otolaryngology, Northwestern University School of Medicine, Chicago. Pp. 302; 90 illustrations and 4 color plates. Philadelphia: Lea & Febiger, 1940. Price, \$3.75.

## NEW EDITIONS

*Neoplastic Diseases. A Treatise on Tumors.* By JAMES EWING, A.M., M.D., Sc.D., LL.D., Professor of Oncology at Cornell University Medical College, New York City; Consulting Pathologist, Memorial Hospital. Pp. 1160; 581 illustrations. Fourth Edition, revised and enlarged. Philadelphia: W. B. Saunders Company, 1940. Price, \$14.00.

*Physical Therapy for Nurses.* By RICHARD KOVACS, M.D., Clinical Professor and Director of Physical Therapy, New York Polyclinic Medical School and Hospital; Attending Physical Therapist, Manhattan State, Harlem Valley State and West Side Hospitals, etc. Pp. 335; 99 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, \$3.25.

*Principles of Hematology.* By RUSSELL L. HADEN, M.A., M.D., Chief of the Medical Division of the Cleveland Clinic, Cleveland; Formerly Professor of Experimental Medicine in the University of Kansas School of Medicine, Kansas City, Kansas. Pp. 362; 104 illustrative cases, and 167 illustrations including 173 original photomicrographs and 100 original charts and drawings. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, \$4.50.

*The Diagnosis and Treatment of Pulmonary Tuberculosis.* By JOHN B. HAWES, 2d, M.D., Late President of the Boston Tuberculosis Association; Director of the National Tuberculosis Association, etc., and MOSES J. STONE, M.D., Assistant Professor of Medicine, Boston University, School of Medicine; Physician to the Chest Clinic of the Massachusetts Memorial Hospital, Boston, etc. Pp. 260; 75 illustrations. Second Edition, revised by DR. MOSES J. STONE, with a Foreword by RICHARD C. CABOT, M.D. Philadelphia: Lea & Febiger, 1940. Price, \$2.75.

*An Introduction to Biochemistry.* By WILLIAM ROBERT FEARON, M.A., Sc.D., M.B., F.I.C., Fellow of Trinity College, Dublin; Member of the Royal Irish Academy. Pp. 475. Second Edition. St. Louis: The C. V. Mosby Company, 1940. Price, \$3.75.

*A Textbook of Physiology.* By WILLIAM H. HOWELL, Ph.D., M.D., Sc.D., LL.D., Emeritus Professor of Physiology in The Johns Hopkins University, Baltimore. Pp. 1117; 330 illustrations. Fourteenth Edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1940. Price, \$7.50.

*Textbook of Biochemistry.* By BENJAMIN HARROW, Ph.D., Professor of Chemistry, City College, College of the City of New York. Pp. 439; 88 illustrations. Second Edition, revised. Philadelphia: W. B. Saunders Company, 1940. Price, \$3.75.

# PROGRESS OF MEDICAL SCIENCE

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## SURGERY.

UNDER THE CHARGE OF  
I. S. RAVDIN, B.S., M.D.,  
HARRISON PROFESSOR OF SURGERY, UNIVERSITY OF PENNSYLVANIA,  
PHILADELPHIA, PA.,

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C. G. JOHNSTON, M.S., M.D.,  
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### SOME OBSERVATIONS ON PERFORATED GASTRIC AND DUODENAL ULCER.

THE mortality from perforated peptic ulcer is still high, despite the advances which have been made in the general postoperative care of patients. Factors which influence the mortality rate in this not uncommon catastrophe are at times difficult to analyze, despite the fact that there is more or less agreement that peritonitis or intra-abdominal abscess is the most usual cause of death.<sup>8,11,22,29a</sup> Most of the published reports are concerned chiefly with benign ulcers which perforate into the free abdominal cavity. Obviously, ulcers which perforate into an area of preformed adhesions, posteriorly into the pancreas, or some other viscus, or preformations of malignant ulcers, present problems which are different from acute perforations of ulcers of the free portions of the duodenum or stomach in which widespread contamination of the peritoneum results.

The reported mortality statistics relating to this latter type are variable and reasons for the variations are not yet clear. Roscoe Graham<sup>13a</sup> reported a mortality of 3% in a series of 60 cases and intimated that the important factor in obtaining such excellent results was the fact that only closure of the perforation was done. Judin<sup>20</sup> reported a mortality rate of 12.8% in 418 cases operated upon for perforated peptic ulcer and suggested that resection of the stomach played an important rôle in attaining this low mortality, since in his experience the mortality decreased steadily as the number of resections increased. Junghanns<sup>21</sup> reported statistics from Schmieden's Clinic which indicated a steadily decreasing mortality in the period from 1914 to 1938. In the period from 1928 to 1938 there were but 3 deaths in 63 cases in which resection of the stomach was performed, a mortality of 4.8%. In the same period 52 cases were treated by simple suture of the ulcer with or without gastro-enterostomy, with 19 deaths, a mortality of 36.5%. While

Junghanns was not willing to ascribe the decrease in mortality solely to the type of operation which was performed, pointing out that in the more recent series the cases were operated upon earlier, he believed that the increased frequency of resections has played a definite rôle. Obviously, here are two diametrically opposed viewpoints regarding the best method of handling free perforations of peptic ulcers, one stating that the simplest procedure in the acute emergency is best and that time ought be taken to prepare the patient for operation, the other that a radical procedure should be performed as early as possible.

Despite the fact that reported statistics of perforated ulcer treated by immediate partial gastrectomy, since the paper by von Haberer,<sup>15</sup> in 1922, indicate mortality rates which are at least as good as those from simple closure, there is well-founded skepticism regarding the advisability of performing a procedure of such proportions in the presence of widespread peritoneal contamination. Since peritonitis offers the threat of major importance to life in these cases it does not seem logical to assume that gastrectomy will decrease its severity, or the possibility of a fatal outcome. It is logical, we believe, to assume that in addition to the deleterious effects of spill from the stomach or duodenum through the perforation, the increased mortality of partial gastrectomy is added and, therefore, the immediate mortality should be higher. Granting that secondary operations may be prevented if partial gastrectomy is performed, the effect on the immediate mortality is of major importance. Graham<sup>13a</sup> has said, "The responsibility of the surgeon is to save life." This object, we agree, can best be obtained by conservative surgical procedures. The advocates of resection in acute perforations<sup>15,20,21,34</sup> stress the importance of the greater relief from ulcer symptoms, following the radical operation, but it is well to note that the necessity for secondary operation following simple closure is not frequent,<sup>10,22,23,30</sup> although the recurrence of ulcer symptoms is not unusual.<sup>28</sup>

The treatment of uncomplicated duodenal ulcer has changed during the past 20 years, especially as regards the concept that duodenal ulcer was predominantly a surgical condition and required some form of operative procedure. Surgical intervention, however, should be reserved for those cases which do not respond to well-controlled medical therapy or in which sequelæ, such as perforation, obstruction, or massive or recurrent hemorrhage are present. Accordingly, following simple closure of a perforated ulcer subsequent surgical therapy should be based upon the same indications.

The method for handling cases of perforated ulcer must be based upon considerations more fundamental than variations in operative approach. The majority of studies on this problem<sup>6,12,21,23,25,29b,31</sup> stress the influence of the amount of time elapsing between perforation and operation. Variations in response to therapy in individual cases indicate that the time interval is not all important, since many patients who were otherwise in good condition die even when operated upon early, while others survive late operation, or even no operation at all. In this regard we have had 3 cases with an unquestioned rupture of a duodenal ulcer, with free air beneath the diaphragm, all of whom refused operation and recovered with no other therapy than supportive measures and constant suction drainage to the stomach. Nagel<sup>26</sup> also

reported a case treated by this method but it is obviously not the therapy of choice. Actually the factor of time is not the sole one. The reaction of the patient to the perforation and the total amount of material spilled are of nearly equal importance. That there is an increase in mortality with increasing period between perforation and operation has been frequently stressed. Time alone is not important, but rather what is happening during the time from perforation to operation.

The patient who drinks large quantities of fluid, whose stomach is lavaged, or who retches a great deal, is more likely to increase the amount of insult to his peritoneum than one who lies quietly, and has an empty stomach at the time of perforation. We have analyzed our own cases, 56 for a period of 1 year, and have noted that while there was the expected tendency toward higher mortality in the late cases, this was not constant, there being a greater mortality in the 4 to 8 hour period than in the 8 to 12 hour period.

The length of time from perforation should not alone be used for prognosis, nor for the decision as to operation in late cases. However, the concept that delay in instituting therapy is deleterious has played an important rôle in the decreased mortality rates. The prevention of delay in therapy is usually not difficult, since the patient as a rule seeks medical aid early. The diagnosis with few exceptions ought likewise be made early, since the onset of symptoms is sudden.

Perforation of a peptic ulcer is one of the most dramatic of incidents and the diagnosis is hardly to be missed. So sudden is the onset that the patient can usually tell the exact time. The associated pain, usually located in the epigastrium, is so acute that the patient lies perfectly still, fearing to move. Rigidity comes on early and is boardlike, especially in the upper abdomen. Despite the excessive pain the patient usually shows no sign of shock except pallor, the pulse and blood pressure as a rule remaining within normal limits. The diagnostic features of perforated ulcer are well described by Moynihan<sup>25</sup> and are therefore not reviewed in detail here. This clear-cut picture is present in about 90 to 95% of cases.<sup>22,23</sup> Rarely the condition may be confused with coronary artery occlusion, pancreatitis, or appendicitis. Vomiting is not usual in ruptured ulcer, but does occur. The fact that the patient has had no previous history suggestive of ulcer ought not be considered unusual, as this not infrequently happens. The number of cases reported without previous ulcer symptoms varies from 5 to 45%.<sup>14</sup> Moynihan<sup>25</sup> has stressed the fact that true surgical shock is not a part of the early picture and should not be expected. Several authors<sup>4,5,33a</sup> have stressed shock as a frequent accompaniment of acute perforations of peptic ulcer either by inference or direct statement. While the patient usually appears "hard hit" and might because of the nature of the accident be expected to be in true surgical shock, blood pressure levels are usually well maintained because of profound vasoconstriction. In our own experience we have rarely seen a picture simulating surgical shock until late when it is ascribable to a fatal peritonitis. This likewise has been the experience of others.<sup>8,22,25</sup>

It has been the general impression that perforated duodenal ulcer constitutes one of the few remaining surgical emergencies which require immediate operation. The few cases in which we have been forced,



because of the patient's condition, to delay operation has suggested to us that when these patients require pre-operative preparation, a few hours' delay may be well spent. This has been well stressed by Graham.<sup>13b</sup> Frequently the ulcer patient is in poor nutritive state.<sup>2,17b,19</sup> Recently the nutritive state of these patients has received attention, not only with relation to healing of the ulcer, but the healing of the wound after operation.<sup>17a,b,32</sup> The operative wound in these cases is prone to become infected or to disrupt. It has been pointed out that difficulty of wound healing in these cases may be associated with the same factors which caused the ulcer to perforate. There is no good reason why ulcers should perforate under ordinary conditions, and there is a suggestion that the perforation might well be due to general nutritive disturbances.<sup>17b,19</sup>

Even in the absence of the usual signs of shock, adequate fluids, blood or plasma should be administered before operation, unless the patient appears to be in very good condition. Emptying of the stomach is of value, provided this can be done without causing excessive retching. As a rule, this can be accomplished by a Levine tube passed through the nose. Occasionally this is effective in decreasing the amount of intraperitoneal spill from the stomach, but it must be remembered that in many cases the patient will have solid particles in the stomach which makes aspiration difficult. No attempt should be made to wash the stomach by the introduction of fluid through the tube because of the possibility of increasing the spill. We have not found it necessary to give soda bicarbonate or Seidlitz powders to increase the subdiaphragmatic gas for diagnosis. The time necessary for preparing the patient for operation need not be long. Preparations should be started as soon as the patient presents himself for treatment and the first step should be centered about keeping the stomach empty, the patient quiet, and the restoration of fluid and salt balance.

The operation should be as simple and as non-traumatic as possible. Graham<sup>13b</sup> stressed the fact that extensive procedures are not necessary to effect a closure of the ulcer and that suturing omentum over the opening is all that was necessary. We prefer closure of the perforation with the sutures left long tying a piece of omentum over the opening. We see no need of extensive exploration in these cases and agree with most authors that the least done at the time of the operation is in the end best. Aspiration of as much of the intra-abdominal content as is easily accessible is of value. We can see no reason for routine drainage of these cases, although this is advocated by some authors.<sup>9,11,24</sup> It is quite impossible to drain the peritoneal cavity, and drains inserted may have the tendency to add additional insult to the peritonium by providing access of bacteria and through direct trauma. There is no doubt that organisms are present in the peritoneal content of cases with free rupture of a duodenal or gastric ulcer.<sup>7,8,11</sup> Where there is a large amount of spill their dilution may be great enough to account for many of the negative cultures that are obtained. It has been stated that the gastric hydrochloric acid is sufficiently bacteriostatic to prevent growth.<sup>33b</sup> That acidity is not the sole factor is suggested by the fact that fluid removed from these cases, even soon after perforation, has a hydrogen-ion concentration approximating the blood plasma.<sup>18</sup> Furthermore, in a series of 20 such cases studied at the

Detroit Receiving Hospital by Dr. Charles M. Henry, the hydrogen concentration of the stomach content at the time of operation was uniformly high, the chloride content low, and this state of affairs has been found to exist for several days after operation.

The operative procedure is greatly simplified in the case of perforated duodenal ulcer by the use of the incision described by Amendola<sup>1</sup> and Hartzell and Sorock.<sup>16</sup> Not only is trauma to the peritoneum minimized but the small transverse incision permits better pulmonary ventilation after operation, reduces the incidence of eviscerations and results in shorter convalescence. Patients operated upon through the incision described by Hartzell and Sorock<sup>16</sup> are able to be discharged after a week, so far as integrity of the wound is concerned.

Since intra-abdominal infection is the most common cause of death in these cases it may be suggested that the introduction of sulphanilamide into the peritoneal cavity, or by hypodermoclysis, as reported by Ravdin, Rhoads and Lockwood<sup>27</sup> for cases of ruptured appendicitis, would be of value. We have not used this procedure routinely in the case of ruptured peptic ulcer, as the incidence of frank infection is not so high as in the cases of perforation of the appendix. In cases operated upon late we feel the procedure has merit.

We prefer to perform the operation with spinal anesthesia because of the relaxation and quietness it affords to the abdominal wall and the viscera. Several authors agree with this choice of anesthetic.<sup>11,13,22</sup> We have not noted that spinal anesthesia causes any increase in the spill of gastro-intestinal fluid. When we have introduced methylene blue into the stomach to outline the perforation<sup>3</sup> we have frequently found that the ulcer site was not colored. Surely if there was a tendency for the extrusion of additional material after spinal anesthesia, the methylene blue ought to leak out freely. We have not felt that the method is of great value, since the perforation is usually not difficult to find.

The perforation of a peptic ulcer is a complication which is in itself but an incident in the general problem of the ulcer patient. It demands early surgical intervention and because of the possibility of peritonitis resulting from such an accident it appears that the less trauma inflicted at the time of operation, the better. Following operation the treatment is similar to that in cases where peritonitis is imminent. Maintenance of fluid and salt balance, continuous decompression of the stomach, bed rest, and plasma or blood transfusions are important. Following recovery from the operative procedure it is well to bear in mind that the patient must be treated as an ulcer patient. While the perforation of a duodenal or gastric ulcer usually has a salutary effect on the patient as regards the manner in which he follows his diet, these patients ought to be considered as the usual ulcer patient and therefore subject to the difficulties incident to the disease. Subsequent surgical procedures ought to be based on the merits of the individual case, without particular reference to whether or not there was a previous perforation.

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## OPHTHALMOLOGY

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## THE PATHOGENESIS OF SYPHILITIC OPTIC ATROPHY.

IN a series of recent papers, Moore and his coworkers<sup>2-4</sup> have reviewed the prevailing conceptions of the nature of the involvement of the optic nerves in syphilis of the central nervous system. They have discussed the pathology and probable pathogenesis of so-called primary optic atrophy and have considered the effects on the progress of the atrophy of modern as compared to older methods of treatment. Though none of the problems connected with this disease can be considered to be finally solved, yet considerable interesting and valuable data have been accumulated.

Syphilis of the central nervous system may involve the optic nerves in three distinct ways. There may be primarily an optic neuritis which may subside without residuals or may result in secondary optic atrophy. There may be an axial or retrobulbar neuritis, the primary expression of which is a central scotoma without visible changes in the optic nerve and the end-result retrobulbar atrophy. Finally, there may be simple (non-inflammatory), progressive, so-called primary atrophy. In the

combined series of Woods and Dunn and Woods and Rowland, quoted by Moore, 45 of 58 syphilitic lesions of the optic nerves (77.5%) were of this last type. Even within this group of simple atrophies, however, considerable clinical variations occur. In most of the cases, the changes in the visual fields are essentially concentric constrictions of varying form. But in some cases the changes in the fields are of bitemporal or homonymous type suggesting involvement of the chiasm or optic tracts. It has been suggested, however, that these latter types of field defects may represent sector-like involvements of the optic nerves proper, rather than actual involvement of the chiasm or tracts. Moore and his coworkers seem to be inclined to consider in a single group all cases of optic atrophy in which there is evidence of more or less diffuse involvement of the nerve and in which there is no ophthalmoscopic evidence of preceding inflammation.

Following the lead of Wilbrand and Saenger, many ophthalmologists have been inclined to believe that simple atrophy of the optic nerve might develop in connection with syphilis of the central nervous system in two rather distinct forms with rather characteristic differences in visual field changes, mode of progression, response to treatment, pathology and pathogenesis. In the first type, there occurred gradual diminution of central vision and progressive contraction of the fields for form and color, the color fields showing greater loss proportionately than the form fields. These changes were taken to indicate diffuse involvement of the nerve, the true tabetic optic atrophy. It was assumed that in these cases the underlying lesion was that suggested by Uhthoff,<sup>5</sup> a primary degeneration of the ganglion cells and nerve fiber layer in the retina which ascended along the optic pathway in a centripetal direction. Secondly, Wilbrand and Saenger described a type of case in which concentric contraction of the form fields occurred while central vision remained normal and color perception was good in the functioning portions of the field. It was assumed that in these cases the intracranial portion of the optic nerves was involved in association with a basal meningitis. In the true primary tabetic optic atrophy, treatment was regarded as useless and even harmful, and blindness was regarded as the inevitable ultimate result. In the cases of the second type, associated probably with basal meningitis, treatment was often successful in arresting the progress of the atrophy.

More recent studies of the pathologic histology of the optic nerves in central nervous system syphilis raise considerable doubt as to whether there is any such basic distinction between types of syphilitic simple optic atrophy. According to Epstein,<sup>1</sup> Léri stated in 1904 that he had found numerous intact ganglion cells in the retina in the presence of complete optic atrophy and that ganglion cells were constantly present, irrespective of the presence or absence of myelinated fibers in the optic nerve. In 1913, Stargardt, quoted by Moore and by Epstein, demonstrated that, in syphilitic simple optic atrophy, the earliest histologic changes were to be observed in the chiasm and intracranial portion of the optic nerve in the form of undue proliferation of the glia fibers in the pial and subpial zones of the nerve, with isolated plasma cells in the overlying pia. Along with increasing infiltration of round and plasma cells in the overlying pia and proliferation of glia fibers in the nerve, degeneration of the medullary sheaths underlying the

infiltrated areas occurred, to be followed later by degeneration of the axis cylinders. The nerve fibers were ultimately replaced by glia cells filled with amyloid. The intraneural connective tissue and the blood-vessels usually were not involved even in far-advanced cases.

Since the work of Stargardt, histologic studies of the optic nerve in syphilitic optic atrophy have been made by Palick-Szanto, Richter, Fujiwara, Behr and Igersheimer. These authors agree that the atrophic process starts in the intracranial portion of the optic nerve and in the marginal fibers of the nerve. Apparently Richter and Palick-Szanto believe that the lesions of the nerve proper are secondary to inflammatory changes in the overlying meninges. Behr thinks that the primary change in syphilitic optic atrophy is an inflammatory process in the glial connective tissue septa of the intracranial portion of the nerve and of the blood-vessels that run in them. He emphasizes the effect of vascular changes on the nutrition of the nerve fibers and thinks the exudative changes in the meninges are coincidental. Igersheimer also is doubtful of the relationship of the degenerative to the inflammatory process. He states that round and plasma cell infiltration of the pia and arachnoid near and around the chiasm and the intracranial portion of the optic nerve is frequent, whether or not optic atrophy is present. He reports 1 case in which there was definite optic atrophy with only minimal cellular infiltration in the pia and none in the septa of the nerve. According to Moore, Fujiwara made histologic studies of the visual pathways in 19 cases of neurosyphilis, in only 2 of which optic atrophy had been demonstrated clinically. Cellular infiltration of the overlying pia was present in 17. Some degree of atrophy of the nerve fibers could be demonstrated in the intracranial portion of the optic nerve in 17, in the chiasm in 11, and in the tracts in 3.

With reference to the rôle played by the direct presence of the organisms in the tissues *versus* a toxin in the causation of optic atrophy, Moore quotes the work of Igersheimer, who searched for treponema in the optic pathways of 40 neurosyphilitics. In 1 of 10 cases in which the optic nerves were normal, a single organism was demonstrated in the optic tracts. Organisms were found in 3 of 9 cases in which there were marked inflammatory changes in the pia about the chiasm and nerves but no degeneration of the nerves, and in 7 of 21 cases in which optic atrophy was present. Experimentally, Igersheimer injected an emulsion of *Treponema pallidum* into the common carotid artery of 4 rabbits. In 3, extensive lesions developed in the choroid and retina with ascending atrophy of the optic nerve secondary to injury to the ganglion cells of the retina. In 1, a moderate degree of optic atrophy developed without marked intra-ocular changes.

In evaluating the work of these various authors, Moore concludes that it has been settled only that optic atrophy starts in the marginal fibers of the intracranial portion of the optic nerve distal to the chiasm. He states that, apparently, the atrophic process bears no direct relationship to the presence or absence of exudative changes in the overlying or neighboring meninges or to the presence or absence of *Treponema pallidum* in or close to the visual pathways.

The most recent report on the histologic changes in syphilitic optic atrophy has been made by Epstein (March, 1940). A man, aged 57, had been blind in the right eye for 20 years and had had progressive

loss of vision in the left eye for 3 months, due to bilateral optic atrophy. Neurologic evidences of tabes were present. The cerebrospinal fluid showed mildly positive findings consistent with a predominantly meningeal type of neurosyphilis. At necropsy the findings were those of chronic syphilitic meningitis rather than of general paresis or tabes. Both optic nerves were adherent to the dural sheath. The optic nerves, chiasm and tracts were extremely thin and were grayish on cross-section. The optic nerves and retinas were studied histologically. The meningeal infiltration seen elsewhere in the nervous system was present in considerable amount throughout the intracranial portion of the optic nerves, the chiasm and the tracts. In front of the orbital foramen it was slight and practically none was seen around the most anterior part of the optic nerves. In the chiasm the entering vessels were all surrounded by cuffs of lymphocytes, but anterior and posterior to the chiasm very few lymphocytes could be found within the parenchyma of the nerve, except in a narrow zone under the pia. Anterior to the optic foramen the subarachnoid space was obliterated and the pia and arachnoid were thickened and adherent in many places to the dura. The connective tissue septa were considerably thickened near the surface of the nerve, but those near the center were less affected. The pia and arachnoid covering the intracranial portion of the optic nerves and tracts were thicker than normal. There was no evident disease of the walls of the small vessels in the optic pathways beyond the infiltration with lymphocytes. In the right optic nerve, demyelination was almost complete. A number of myelin sheaths could be seen in the most anterior portion of the nerve, but these disappeared farther back. Near the optic papilla they were associated with a much larger number of axis cylinders scattered fairly evenly through the core of the nerve but scanty near its surface. Most of these axis cylinders disappeared also in the region of the optic foramen. In the left optic nerve, demyelination was greatest on the surface but there was a sector of destruction which penetrated deeper into the nerve. There was a considerable paucity of myelin sheaths even in the core of the nerve. Axis cylinders were more numerous than myelin sheaths and were present even in areas of complete demyelination. Behind the chiasm the right optic tract contained many fewer myelinated fibers than the left. Both retinas showed great loss of nerve cells and fibers in the inner layer. In the right very few nerve cells remained; in the left a considerable number were preserved in the neighborhood of the macula. The granular layers and the rods and cones were well preserved everywhere. There was a moderate excess of neuroglial fibers in the nerve fiber layer. The optic nerves showed intense neuroglial sclerosis throughout their intra-orbital course.

In this case, Epstein summarizes, there was diffuse thickening of the leptomeninges with infiltration with lymphocytes. Lesions were present in the optic nerves, chiasm and tracts. There was good evidence of a fairly close relationship between the inflammatory and degenerative reactions in the nervous system. These observations suggest that chronic meningeal inflammation is the cause of optic atrophy. The position of the crossed nasal fibers on the meningeal surface of the optic tracts makes them more liable to be affected by inflammation. This may explain the tendency to bitemporal hemianopsia in certain cases.

It would seem, then, that in the opinions of most of the recent students of the pathologic anatomy of syphilitic optic atrophy the conception of the atrophy as a primary degenerative process is giving way to the idea that it is secondary to inflammation, either in the surrounding meninges or in the nerve itself. One objection to this concept of the primary influence of inflammation in the production of optic atrophy lies, however, in the frequency of occurrence of optic atrophy in the various forms of neurosyphilis as classified by Moore. In the early form of meningeal neurosyphilis, acute syphilitic meningitis or neurorecurrence, involvement of the optic nerve is frequent in the form of optic neuritis or neuroretinitis. This is supposed to subside without residuals, however. In late syphilitic meningitis, discrete or diffuse gummatous infiltration of the meninges, especially about the base, optic atrophy does occur at times, apparently. In meningo-vascular or cerebrospinal neurosyphilis, the occurrence of optic atrophy is questionable. In vascular neurosyphilis, the type characterized by cerebrovascular accidents, optic atrophy is uncommon. It is in parenchymatous neurosyphilis that optic atrophy is most frequently encountered. And it is worthy of note that optic atrophy occurs less frequently in pure paresis, in which organisms are readily demonstrable in the tissues in large number, than in pure tabes, in which organisms can be demonstrated rarely if at all. These facts have led to the concept that optic atrophy results from a toxic rather than an inflammatory affection of the nerve fibers.

In recent years, several new theories of the pathogenesis of syphilitic optic atrophy have been advanced and supported by various authors. These various theories have been critically considered by Moore and Woods in their most recent contribution on the subject of syphilitic optic atrophy. It is of interest to review these theories in the light of the criticisms proposed by Moore and Woods.

Abadie advanced the theory that optic atrophy developed as a result of a nutritional disturbance of the nerve due to syphilitic involvement of its blood supply. He noted that, in many cases of tabetic optic atrophy, the retinal arteries were constricted. He thought that this was due to a disturbance of the sympathetic nervous control of the central artery of the retina by a lesion in or near the ciliospinal center in the medulla similar to that causing the Argyll-Robertson pupil. The constriction of the vessels was believed to be progressive and permanent, thus leading to progressive ischemia of the retina and optic nerve and to ascending degeneration of the nerve. In the opinion of Moore and Woods, no proof of the validity of this theory has been advanced from a pathologic, clinical or therapeutic standpoint. The administration of atropine or acetylcholine and the employment of carotid or cervical sympathectomy have not been demonstrated to control the advance of the atrophic process. Along these same lines, Hamburg suggested that optic atrophy was due to lowered cellular metabolism and oxygen utilization in the optic nerves of tabetics and proposed treatment by thyroxin and by potassium permanganate intramuscularly. Loeffler used this method also with questionable results. Saitzew recommended the administration of placental blood subcutaneously in the treatment of optic atrophy because of the richness of this blood in hormones and in biologic activity.

An explanation of the pathogenesis of syphilitic optic atrophy which received considerable acceptance and support for a time at least was that advanced by Lauber and Sobanski. They contended that the atrophy results from a disturbance in the nutrition of the optic nerve or retina due to a change in the relationship between systemic blood pressure, retinal arterial blood pressure, and intra-ocular tension similar to that observed in cases of pseudoglaucoma. The normal differential between intra-ocular tension and retinal arterial diastolic pressure should be at least 14 mm. of mercury. If this differential falls, there is disturbance in the capillary circulation with resultant poor nutrition of the retina and optic nerve. All tabetics with optic atrophy suffer from peripheral hypotension, diastolic, at least, if not systolic as well. As a result, retinal diastolic arterial pressure, which averages about 45% of systemic diastolic pressure, approaches the level of intra-ocular tension, 18 to 26 mm. of mercury, circulatory failure in the optic nerve results, and optic atrophy develops. In tabetics without optic atrophy the systemic blood pressure is normal or elevated. Peripheral hypotension is caused in many instances by the presence of syphilitic aortitis with a dilated aorta. These authors assert also that all the drugs used in the treatment of syphilis, such as arsenic, bismuth, mercury, iodides, and fever therapy, tend to lower the blood pressure. Since it is impossible to maintain an elevation of the blood pressure by therapy of any sort, the treatment of syphilitic optic atrophy should be essentially that of glaucoma, miotics and, if these are ineffectual, cyclodialysis. According to Sobanski's figures, in 33 patients with optic atrophy, the differential between retinal arterial diastolic pressure and intra-ocular tension was 18 or less in 29, and less than 14 in 7. In 9 tabetics without optic atrophy, the differential was 19 or more. In his latest report on 110 eyes, 13 were blind before treatment was started and showed no improvement. Of the remaining 97 eyes, 51 improved, 26 became worse, and 20 showed no change. No patient was observed for longer than 3 years, and all had some form of anti-syphilitic treatment; some received malaria.

According to Moore and Woods, a number of observers have studied cases along the lines suggested by Lauber and Sobanski. While a few of these have confirmed their results, most have been unable to do so. There is no actual proof of the efficacy of treatment along these lines. The fact that optic atrophy does not occur in conditions such as Addison's disease with prolonged hypotension is also a strong argument against this theory. The figures presented by Langhammerova and by Ascher furnish the most convincing proof of the incorrectness of this theory. Langhammerova showed that of 59 tabetics with optic atrophy, 69.4% had normal blood pressure, 23.7% had hypertension, and only 6.7% had hypotension. Of 94 tabetics without optic atrophy, 53.2% had normal blood pressure, 22.3% had hypertension, and 24.4% had hypotension. According to Ascher, in 23 patients with tabetic optic atrophy, the systemic blood pressure averaged 133/81 in mm. of mercury, the retinal arterial diastolic pressure averaged 42.1 mm. of mercury, and the intra-ocular tension averaged 18.6 mm. of mercury. The differential then averaged 23.5 mm. of mercury. In 28 tabetics without optic atrophy, the systemic blood pressure averaged 131/82 in mm. of mercury, the retinal arterial diastolic pressure averaged 40.2 mm.



of mercury, and the intra-ocular tension averaged 19.07 mm. of mercury. The differential then averaged 21.13 mm. of mercury. These figures certainly do not lend any support to the contentions of Lauber and Sobanski.

Since the original report by Balado and Satanowsky in 1939, considerable attention has been paid to the question of the production of progressive optic atrophy by so-called optochiasmal arachnoiditis. It is assumed that, in the course of a primary inflammation of the meninges, an arachnoiditis develops around the optic nerves and chiasm. The inflammatory tissue in the arachnoid surrounds and compresses the optic nerves and chiasm and fixes them to the neighboring structures, sometimes with the collection of serous fluid in the form of arachnoidal pockets or cysts. These lesions cause constriction of the nerves and their blood supply, as a result of which atrophy develops. The only effective treatment for this condition, at least in its more advanced phases, is surgical. A certain number of cases of syphilitic optic atrophy have been included among the reports of this condition. That all cases of optic atrophy in syphilis are manifestations of optochiasmal arachnoiditis seems rather difficult to believe.

In their critical review of the reports on optochiasmal arachnoiditis in syphilitic optic atrophy, Moore and Woods state that practically all cases have been inadequately studied and that too many cases have been reported on presumption and without verification. The results of surgical treatment are not very satisfactory. However, in the light of our present knowledge, it would seem worth while to advise surgical intervention in patients with syphilitic optic atrophy, with or without classic chiasmal type field defects, if the atrophy is progressing in spite of modern antisymphilitic treatment by the subdural method or with malaria. Surgery is perhaps especially indicated in cases of optic atrophy in neurosyphilis without frank signs of tabes.

A fourth pathogenetic theory that deserves consideration is that tabes and optic atrophy are the result of combined syphilis and nutritional deficiency. Moore and Woods review the reports in the literature on the occurrence of optic nerve lesions in clinical and experimental vitamin deficiency. They conclude that it seems reasonably clear that in experimental animals at least, degenerations may occur in the spinal cord and sometimes in the optic nerves as a result of diets deficient in vitamin A, vitamin B, or both. With diets deficient in vitamin A, the degeneration is spotty in nature and is not sharply localized to the posterior columns of the cord. With diets deficient in some part of the B complex, the degeneration in the cord is sharply limited to the posterior columns and the lesion is indistinguishable from that of tabes. There is conflicting evidence as to the involvement of the optic nerves in deficiencies of vitamins A and B, but apparently degeneration of the optic nerves can be produced by some form of deficient diet. The particular component responsible is not clear as yet. The development of tabes and optic atrophy may depend conceivably on a combination of neurosyphilis and dietary deficiency, but, if so, the dietary deficiency must relate to a time period before the patient comes under observation. The deficiency of any particular element may depend on improper metabolism rather than on the absence of this element from the diet. These facts make it difficult to investigate cases of optic atrophy

clinically along the lines of nutritional deficiency. Much further study will be necessary before this theory can be accepted.

One fact that suggests that the lesion which leads to progressive atrophy of the optic nerves may be primarily inflammatory rather than primarily toxic or degenerative is that it is possible to arrest the progress of the atrophy in a certain percentage of the cases, particularly in the early stages, by modern methods of antisypilitic treatment. In 1932, Moore stated that arsphenamine and its immediate derivatives have no deleterious effect on the structures of the eye, but that their routine use does not check the progress of the atrophy and occasionally a Jarisch-Herxheimer reaction occurs in the nerve with rapid loss of vision. Much better results are obtained, however, when arsphenamine is used by approved subdural methods. Of 138 cases of optic atrophy treated by various men by the subdural method, 54% were improved or arrested, while 46% continued to progress. Of 89 cases treated with malaria, 39% were improved or arrested, while 61% continued to progress.

With reference to the use of tryparsamide, Moore stated that 10% of the patients treated with this drug develop blurring or dimness of vision which may clear up or may remain permanent. In a few cases, after discontinuing the drug, a slowly progressive constriction of the visual fields and an increasing pallor of the optic disks may develop, which may be confused with true syphilitic optic atrophy. Differential diagnostic points are that, in the progressive atrophy developing from tryparsamide, the optic nerves and vision were normal before treatment was started, that subjectively the onset of loss of vision occurred in direct relationship to treatment, that the progress is slower than in true syphilitic atrophy, and that central vision returns to its previous level within a few weeks after the onset of the reaction and remains normal in spite of progressive constriction of the fields. Moore believes that tryparsamide is more likely to cause damage to vision in patients in whom the optic nerves are actually or potentially diseased. He treated 12 patients with optic atrophy with tryparsamide. The drug seemed to have a deleterious effect in only 4 of the 12, but it did not arrest the atrophy in the other 8. Hence, Moore is opposed to its use in cases of optic atrophy.

In a more recent paper which appeared in 1938, Moore and his coworkers present figures on the treatment of optic atrophy in which the results, though estimated on a somewhat different basis, seem even more favorable than those given in his earlier paper. The results of treatment in the later paper are estimated on the basis of the number of patients in whom the atrophy progresses to blindness within a certain period of years, "blindness" being considered as vision of 10/200, or less, in the better eye. No specific mention is made of the involvement of the peripheral fields of vision in these cases. Moore and his coworkers state that among patients with syphilitic optic atrophy who receive no treatment at all or inadequate routine treatment (which is defined as less than 10 injections of a trivalent arsenical and 10 injections of a heavy metal), 32% are blind within 1 year, more than 50% in 2 years, more than 75% in 4 years, and all except the rare patient with unusually slow progression are blind within 7 years. To be regarded as successful, any form of treatment must, in their opinion,

delay the development of blindness in a significant proportion of cases or must prevent it beyond the seventh year. When the optic atrophy is unilateral when the patient is seen first, treatment must prevent the development of blindness in the other eye. Among patients who received adequate routine treatment (defined as more than 10 injections each of a trivalent arsenical and a heavy metal), 69% were blind by the ninth year. Among patients who received subdural or intracisternal injections of arsphenaminized serum plus adequate routine treatment, only 53% were blind by the tenth year. Among patients who received malaria plus adequate routine treatment, only 14.6% were blind within 9 years. Seven of 8 patients with unilateral optic atrophy treated subdurally or with malaria did not develop atrophy in the other eye during periods varying from  $2\frac{1}{2}$  to 8 years. Moore and his coworkers conclude, therefore, that the progress of primary syphilitic optic atrophy may be completely arrested by the use of either subdural treatment or malaria, more often by the latter.

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\* A complete bibliography may be found in the articles by Moore and his coworkers.

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ORIGINAL ARTICLES.

DYSPHAGIA WITH DISORDERS OF THE HEART AND  
GREAT VESSELS.

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AN instance of difficulty in swallowing associated with great enlargement of the left auricle (to be described below) drew our attention to the whole question of dysphagia in disorders of the heart and aorta. Since most of the easily accessible statements are inadequate, a brief review of the subject seems in order. It may be said in advance that dysphagia has been described in the following cardiovascular conditions: 1, Dilation of the left auricle (usually with mitral stenosis); 2, pericarditis; 3, saccular aneurysm; 4, dissecting aneurysm; and 5, anomalies of the aortic arch or of the great vessels springing from it. The difficulty in swallowing is usually related to direct pressure on the esophagus (see below) but marked compression frequently exists without any interference with deglutition; in fact dysphagia in cardiovascular disease is a rare event.

The term "dysphagia" has been applied in the literature not only to actual *difficulty* in swallowing but also to *pain on swallowing* without any feeling of obstruction. Dysphagia may be due to compression or to spasm. In the latter event, the contraction is mediated reflexly through the vagus. In either case, as will be seen below, symptoms may be persistent or transient. In order to understand the various clinical conditions which will be described it is important to have in mind the relations of the various cardiac chambers, the aorta and the pulmonary artery and veins to the vagus, recurrent laryngeal nerve, trachea and esophagus. These are pictured in

the following dissections (Figs. 1 and 2). In Figure 1 the close relation of the arch of the aorta and of the whole thoracic aorta to the esophagus is well demonstrated, and in Figure 2 one sees how the left auricle lies in contact with the gullet.

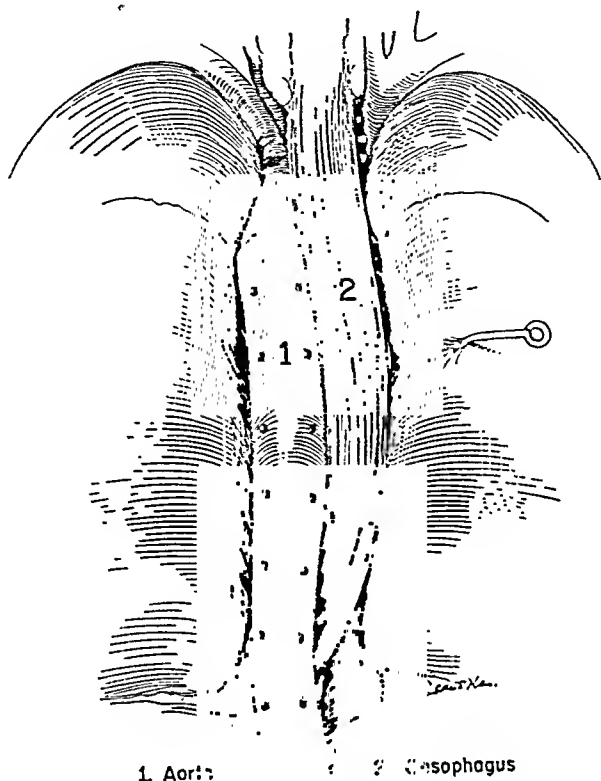


FIG. 1.—Relation of aorta to esophagus. (After Sibson.)

**Dysphagia From Pressure of Dilated Left Auricle.** Great dilation of the left auricle with mitral stenosis is the subject of quite a voluminous literature, and the question of big auricles in relation to recurrent laryngeal nerve palsy and to hoarseness has been especially discussed. One may refer to the article of Kovacs and Stoerk<sup>13</sup> who describe the relations of the esophagus to cardiac enlargement and point out that compression practically never gives rise to dysphagia because of the elasticity and motility of the tube. Excellent papers on the anatomy of big left auricles are also those of Stoerk,<sup>34</sup> whose illustrations have been frequently copied in the literature, and of Steele and Paterson.<sup>35</sup> The cuts here modified from those of Stoerk (Figs. 3, 4 and 5) show very well that the left auricle really has a posterior position and that it impinges, when enlarged, directly on the esophagus as well as upward against the bronchi which may be gouged apart just below the bifurcation. The radiologic literature also is rich in studies of these relations which are particularly well

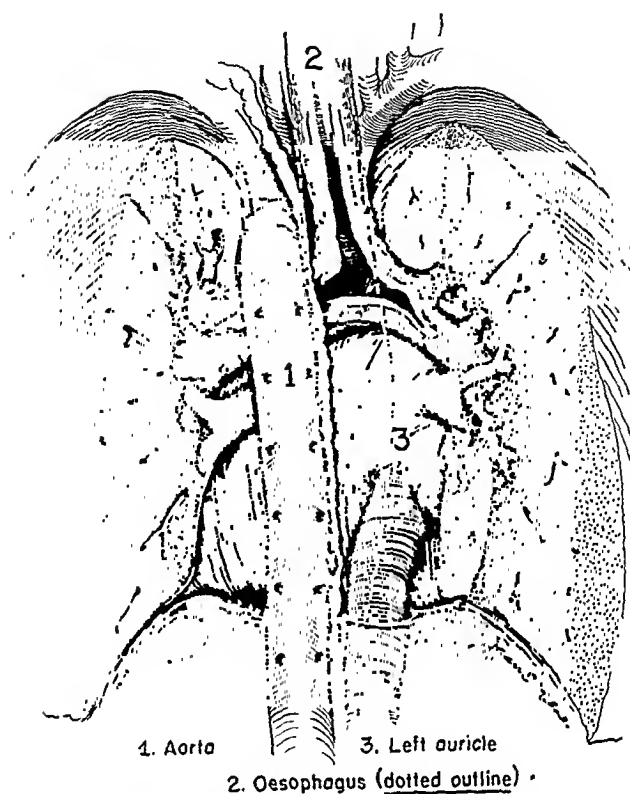


FIG. 2.—Relation of left auricle to esophagus. (After Sibson.)

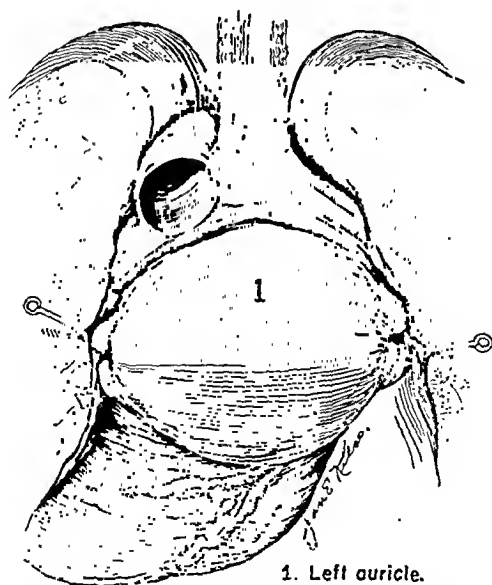


FIG. 3.—Diagram showing large left auricle pressing on bifurcation of the trachea. (Modified from Stoerk.)

exposed by Rösler and Weiss.<sup>24</sup> That compression of the esophagus by an enlarged left auricle is common enough is shown by radiograms to be found in every Roentgen ray laboratory and reproduced in all

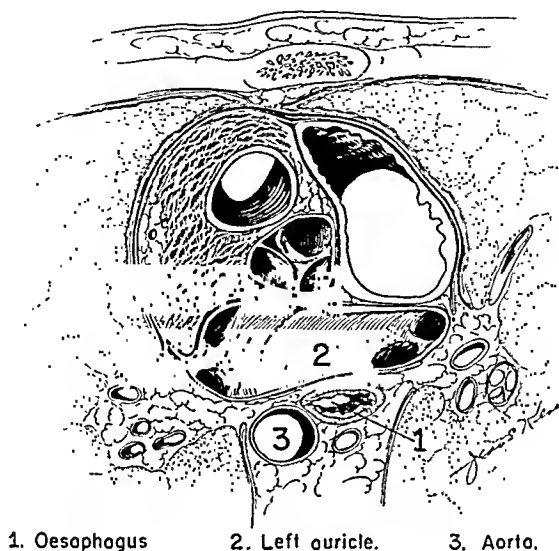


FIG. 4.—Diagram of section through heart, showing posterior portion of left auricle in relation to aorta and esophagus. (Modified from Stoerk.)

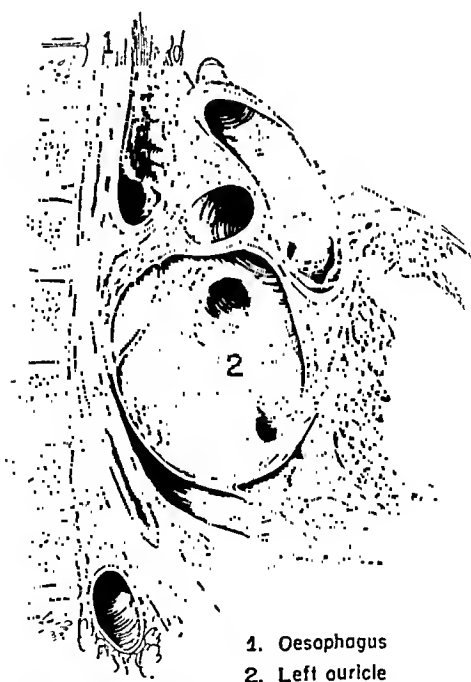


FIG. 5.—Diagram showing large left auricle from a case of mitral stenosis pressing on esophagus. (After Stoerk.)



FIG. 6.—Patient G. A., showing compression of the esophagus by the left auricle and stasis of barium.





the textbooks of cardiology. The radiogram from our patient is typical. Finally one may refer to such articles as those of Bland, Balboni and White<sup>5</sup> who describe the extraordinary capacity attained by dilated auricles. They point out that figures of over a liter have been reported in several cases.

But while compression of the esophagus by the auricle often occurs, clinical dysphagia from this cause is excessively rare. Dysphagia is mentioned, to be sure, in textbooks but only as part of a catalogue of symptoms handed on from one writer to another without any basis of actual experience. As a matter of fact, aside from our case, we have found only two instances in the literature: Cases 1 and 4 of Rösler. The first of these for a year had difficulty in swallowing even water; Roentgen ray demonstrated definite arrest of the barium in a dilated esophagus above the point of pressure. In the other case, there was difficulty only on excitement or exercise, but the Roentgen ray showed delay in passage of barium. Steele and Paterson<sup>33</sup> remark that dysphagia from auricular pressure is "common in the experience of many" but they report no cases of their own nor can we find mention of dysphagia in the papers to which they allude. Notkin<sup>17</sup> in a clinical abstract of 70 cases of big auricle with hoarseness found no mention of dysphagia and in the Index Medicus from 1927 to 1939 there is only one suggestive title,<sup>36</sup> unfortunately not accessible, in a Czech journal.

**Case Report.** G. A. (A92950), a 37-year-old Chinese waiter, entered the Stanford Clinic on November 1, 1939, with the complaints of shortness of breath and pain and difficulty in swallowing. About 13 months ago he began to be conscious of palpitation which was present all the time but was worse on exertion. He was, however, able to go on with his work as a waiter. There was no cough or edema, and his general health was unimpaired. In July, 1939, about 4 months ago, he began to have a sense of discomfort in the lower substernal region on swallowing. It seemed as though the food passed down more slowly than usual and while passing it caused pain or soreness. Frequently 8 or 10 minutes after swallowing he would regurgitate a portion of the food which did not taste sour. He thinks liquid food caused less soreness than a full diet. After 2 months the symptoms subsided, but about 2 weeks ago the pain on swallowing returned and has been present ever since. He has also become more short of breath although he still has no cough, edema or abdominal pain.

On examination he was neither short of breath nor cyanotic as he lay in bed. There were classical signs of mitral stenosis with great enlargement of the heart. There were no signs of pulmonary edema or of congestive cardiac failure.

Roentgen ray study by Dr. Leef on November 3d showed that when the patient swallowed barium the column was pushed back by the enlarged heart and the passage of barium through the esophagus was slow because of this pressure. A film (Fig. 6) showed an immense heart with especial enlargement of the left auricle.

On rest and venesection he improved rapidly and within a few days the dysphagia was less marked and at times disappeared. On November 10th further Roentgen ray studies by Dr. Newell were reported as follows:

"Dr. Bloomfield, Dr. Chamberlain, Dr. Olsen and Dr. Norwood looked over my shoulder while I studied the patient again fluoroscopically. Along

the left border one could make out 4 arches, counting from below upward, the left ventricle, the left auricle, the pulmonary artery and the aorta. Pulsation of the pulmonary artery is not so very marked, even as seen more prominently when the patient turns slightly into anterior oblique. The left auricle as seen in anterior projection occupies two or three times the space ordinarily occupied by the left auricular appendix, and pulsates visibly.

"Still looking with the patient straight front, we see on the lower right border a see-saw motion, the lower portion being evidently right auricle, the upper portion left auricle which is blown out with every systole by regurgitation through the mitral valve. The pulmonary vessels pulsate much more than normal, especially at the right hilum.

"On turning the patient in the left anterior oblique, and true oblique, the thickness of the heart is seen to be very great, so that it cannot be separated from the spine.

"On this occasion the patient swallows thick and thin barium mixture with the greatest of ease. The appearance of the esophagus is perfectly normal. It is indented at the aortic arch and behind the left auricle, of course. The width of the esophagus when the patient drinks barium rapidly, lying supine, is about two and one-half centimeters. As seen in lateral view with the patient lying on his side, drinking thin barium rapidly, the esophagus is seen to be only a few millimeters through from front to back behind the left auricle, although it reaches a diameter of a couple of centimeters above this. In left anterior oblique the course of the esophagus passing the left auricle shows very nicely how much it bulges to the left and backward above the left ventricle."

The patient was discharged on November 14th still complaining of a slight feeling of difficulty on swallowing.

It was the impression of those who studied the case that the dysphagia was due to spasm of the esophagus secondary to pressure by the enlarged auricle, rather than to actual obstruction.

**Dysphagia With Pericarditis.** Most textbooks include dysphagia among the possible symptoms of pericarditis but give no detailed data. It seemed of interest therefore to turn to the periodical literature. Smith and Willius<sup>31</sup> in a clinical analysis of 113 cases of pericarditis make no mention of dysphagia, nor do Camp and White<sup>6</sup> in a study of 106 cases. Harvey and Whilehill<sup>11</sup> in a recent article on tuberculosis of the pericardium also have nothing to say on trouble with swallowing. In the Quarterly Cumulative Index from 1927 to 1939 we found only one allusion to the subject, a brief case report by Rutherford<sup>25</sup> of an old woman with dry pericarditis who had severe pain on swallowing which disappeared as she got well. Capps makes no allusion to dysphagia in his monograph on pericardial pain.<sup>7</sup>

The paucity of information in the modern literature is in contrast to the detailed accounts of dysphagia with pericarditis to be found in the older treatises. Testa (*Delle Malattie del Cuore*, Bologna, 1811) is given credit by Walshe<sup>37</sup> for first describing this difficulty but Stokes<sup>35a</sup> criticizes the case reports and believes the dysphagia was due to cervical abscesses. Stokes further informs us that a thorough search of the works of Senac, Corvisart, Bertin, Laennec, Bouillaud, Hope and Andral yields no allusion to dysphagia. Stokes

himself, on the other hand, refers to a woman of 60 with pericarditis and "as the mouthful of food or drink passed . . . it excited a feeling of tearing or burning . . . which immediately subsided on the ingesta reaching the stomach" (p. 55). Walshe states that he has seen some five or six very striking examples. Sibson<sup>30</sup> distinguishes clearly between discomfort on swallowing presumably due to irritation of the inflamed pericardium by the bolus of food as it passes down the esophagus and actual obstruction of the tube by a distended sac. "There was difficulty or pain in swallowing in 13 of my cases of rheumatic pericarditis. . . . I have already spoken of cases in which the act of deglutition caused pain over the back of the inflamed pericardium, generally complained of, however, in the chest, by the pressure of the morsel of food upon the inflamed structures. . . . The difficulty in swallowing, of which I now speak, occurs when the pericardial sac is distended to the full with fluid, and is caused by the compression of the esophagus between the swollen sac and the spinal column. . . . when the patient lies flat the weight of the fluid in the pericardium falls backward with full pressure upon the esophagus and deglutition becomes more difficult; when, however, he is raised into the sitting posture, and especially if he leans forward the volume of the liquid tends forward and downward and swallowing is more easy." One patient "when the amount of effusion into the pericardium was great, swallowed more easily when the shoulders were raised than when she was lying flat." The subject is further developed along these lines by Roberts.<sup>22</sup>

In summary, then, dysphagia with pericarditis seems to be a rare event. Actual difficulty in swallowing probably occurs only when the esophagus is compressed by a large effusion; hence in the presence of pericarditis dysphagia may be of practical diagnostic importance as to the amount of fluid.

**Dysphagia With Saccular Aneurysm.** In contrast to what has been said in connection with pericarditis and big auricle, dysphagia is recognized by all to be a frequent symptom with saccular aneurysm. But here again it has been noted that even with marked compression of the esophagus there is often no complaint of trouble on swallowing. Stokes<sup>35b</sup> nearly a hundred years ago gives a thorough discussion of the subject. He noted that dysphagia though not uncommon is less frequently observed than compression of the air passages. He never observed it with aneurysm of the ascending arch but did with sacs of both transverse and descending aorta. Occasionally, dysphagia was the patient's sole complaint. Of special interest are Stokes' remarks on the location of discomfort on swallowing. "It is commonly referred to the middle third of the sternum, but may be felt lower down. And in the same case, as has been shown by Dr. Law, it may be referred, successively, to different portions of the tube—now at the top of the sternum, and again to the epigas-

trium." This observation we have verified in connection with pain produced by experimental distention of the esophagus.<sup>20</sup> "The difficulty of deglutition varies from complete dysphagia, which is rare, to the slightest feeling of obstruction; generally fluids are most easily swallowed. The sensation may be merely one of pain. . . . The attempt to swallow often produces a paroxysm, compounded of retching, convulsive hiccough, laryngeal cough, and dysphagia." Nothing worthy of note has been added by subsequent writers. Powell<sup>21</sup> observed cases of aneurysm in which an actual perforation of the esophagus occurred without preceding dysphagia. Balfour<sup>2</sup> suggested that slight difficulty in swallowing arose from some interference with esophageal innervation rather than from actual compression. He also notes that aneurysmal dysphagia varies from time to time, that it is increased by any "excitement of the circulation," and that it may be relieved by leaning forward. Osler<sup>19</sup> felt that actual compression was unusual and that dysphagia was due to spasm via the vagus. Modern texts have much less to say; White,<sup>39a</sup> for example, makes bare mention of dysphagia along with a list of other symptoms. Turning to recent clinical reports, Sanford<sup>27</sup> in a series of 71 cases noted dysphagia in 14; in 2 cases it was the main symptom. Kampmeier<sup>12</sup> among 633 instances of saccular aneurysm found dysphagia in 11%, whereas Mills and Horton<sup>16</sup> in a somewhat comparable study of 339 cases noted this symptom in only 1.2%. Unfortunately no individual case reports are given.

Among our own material are 2 cases of aneurysm in which dysphagia was a notable symptom. In one the patient was unable to swallow solid food and liquids went down only with difficulty; at autopsy, there was an aneurysm of the ascending arch, compression of the trachea, and a false aneurysm with infiltration of blood about the esophagus. In the second case, the man complained of both discomfort and difficulty on swallowing; *post mortem*, there was aneurysmal dilation of the ascending, transverse and descending thoracic aorta with erosion of the aneurysm into the mediastinum and esophagus. In Stokes' most striking case, also, a man with severe prolonged aneurysmal dysphagia, there was found at autopsy a large false aneurysm with the esophagus "strongly compressed by this tumour."

In summary, then, several points of interest emerge: it appears that mild dysphagia, usually due to reflex esophageal spasm, is common with aneurysm and of no serious import; severe persistent dysphagia seems to indicate false aneurysm, or threatened rupture into esophagus, in brief, a condition of the greatest gravity. Such dysphagia in the presence of aneurysm has, therefore, considerable diagnostic and prognostic importance.

**Dysphagia With Anomalies of the Great Vessels.** Dysphagia with right-sided aortic arch, double aortic arch, and aberrant right subclavian artery has been so well described and the mechanism is so

simple that we shall make only brief reference to it here. The papers of Arkin<sup>1</sup> and of Metzger and Ostrum<sup>15</sup> may be consulted for excellent radiograms and diagrams of the anomalies. Suffice it to say that the aberrant vessel causes the symptoms by compression or displacement of the esophagus from behind. Diagnosis can often be made by Roentgen ray and the paper by Arkin is especially thorough from this standpoint.

A philologic digression may be allowed in connection with the term *dysphagia lusoria* which is so frequently applied to the troubles of deglutition encountered with these anomalies. Sprague, Ernlund and Albright<sup>32</sup> attribute the term to Bayford (1789) and point out that *lusoria* is derived from Latin *lusor*, a deceiver; White<sup>39b</sup> refers in this connection to "*dysphagia* (called *lusoria*, from the Latin, meaning deceitful)." Now deceitful dysphagia is meaningless, if not actually nonsense, and some other explanation of the term is required. The expression is obviously a variety of *ellipsis*, common in Latin and Greek, and in medical terms derived from those languages; one thinks quite readily of such expressions as *tabes mesenterica*, *keratitis neuroparalytica*, and *exophthalmic goiter*. The last refers, of course, not to a goiter containing eyes which protrude from it but to a goiter in a pop-eyed person. In other words, the adjective indicates some quality in the person who has the "struma" or "keratitis" of "dysphagia." Now *lusor* or *lusus* is used not only for deceit or playfulness but also for a sport or freak—*lusus naturæ* = a freak of nature—and it seems clear that *dysphagia lusoria* means not deceitful dysphagia but dysphagia in a person who has a freak condition, namely an anomaly of the great vessels. That the older writers with a classical education took this meaning for granted is witnessed by Hilton Fagge<sup>8</sup> who says, "So-called dysphagia lusoria demands a word of notice. The term was first applied by Dr. Bayford of Lewes to a case in which the right subclavian artery arose from the third part of the aorta, and passed to its distribution between the esophagus and trachea. This *lusus naturæ* was probably a mere coincidence since many people with these anomalies have no difficulty in swallowing."

The original report of Bayford<sup>3</sup> is of great interest. Jane Fordham was observed from infancy to have difficulty in swallowing. "For the last twenty years of her life this poor creature could scarcely, from day to day, muster up resolution to force down food to prevent her starving, so much was the difficulty of swallowing now increased. This difficulty she described as arising from an obstruction in that part of the esophagus which is opposite the first bone of the sternum. The food did not return when it came to that place; but seemed to make a momentary stop; and in the instant she felt an inexpressible something approaching to strangulation or suffocation which she could only compare to the conceived agonies of death. Upon these occasions she always experienced violent palpitations of the heart.

I was by accident upon the spot at the time of her death; and having heard the above history of her case, I felt myself interested in making a further enquiry into the cause of the obstruction by an examination of the dead body. . . . If the reasoning which I have used upon this occasion be at all conclusive, and the unusual situation of the right subclavian artery be considered as the sole cause of the obstruction in deglutition; a new species of dysphagia is hereby established, which may be called *lusoria* from the *Lusus naturæ* that gives rise to it."

**Dissecting Aneurysm.** Pressure on the esophagus by the false sac must be a common event in cases of dissecting aneurysm, but clinical dysphagia rarely occurs. As with some of the disorders we have already discussed, general statements about trouble with swallowing are to be found but specific case reports are rare. Shennan,<sup>29a</sup> for example, in his excellent monograph on dissecting aneurysms notes that "In addition to the cases complaining of choking sensations or as if some foreign body had stuck in the throat, there are other cases which complain of difficulty of swallowing, this resulting from direct pressure of the sac upon the esophagus or from involvement of the inferior laryngeal." But no mention of dysphagia is found in the case reports of Shennan's 17 patients. Gager<sup>9</sup> and McGeachy and Paullin<sup>14a</sup> in their analysis of several hundred cases quote no specific instances. We have also looked up the reports of 60 cases<sup>4,10,14b,18,23,26,28,29b,38</sup> in recent papers without finding definite mention of difficulty on swallowing. It may be that dysphagia is overshadowed by other more desperate symptoms such as pain and collapse, or perhaps inquiry is not usually made. At any rate, dysphagia plays no important part in the symptomatology of dissecting aneurysm, although careful questioning as to its presence would be of interest in suspected cases and might help in differentiating from coronary occlusion.

**Summary.** 1. Dysphagia may occur in connection with the following disorders of the heart and aorta: Dilated left auricle, pericarditis, saccular aneurysm, dissecting aneurysm and anomalous aortic arch.

2. While pressure on the esophagus is common with all these conditions, clinical dysphagia occurs very rarely except with saccular aneurysm and anomalous aortic arch.

3. Difficulty in swallowing with pericarditis suggests a large effusion.

4. Marked dysphagia with aneurysm suggests a false sac or huge lesion with threatened rupture.

5. Dysphagia in a supposed case of coronary occlusion should arouse suspicion of dissecting aneurysm.

6. The literature dealing with the above conditions is reviewed and a case of dysphagia associated with compression of the esophagus by an enlarged left auricle is reported.

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## FURTHER EXPERIENCE WITH GLOBIN INSULIN.

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RECENTLY published results<sup>1</sup> indicate that in some moderately severe and severe cases of diabetes, globin insulin has advantages over protamine insulin. The following data on 4 severe cases afford further confirmation.

**Case Abstracts.** CASE 1 (No. 593117).—A man, aged 57, entered the hospital for amputation of the foot due to diabetic gangrene. Although an exceptionally severe diabetic, he had consistently neglected diet and insulin



for 13 years, and overindulged in alcohol. He had marked diabetic retinitis and arteriosclerosis. During the 10 days preceding operation his diet was 150 carbohydrate, 80 protein, and 100 fat, and he received protamine insulin beginning with 40 units and increasing to 100 units each morning, together with varying amounts of regular insulin. Yet he passed sugar continuously with blood values ranging between 210 and 344 mg. per 100 cc. After the operation protamine insulin was increased to 120 units a day and as much as 90 units of regular insulin was given in addition without any effect; that is, all specimens contained maximum amounts of sugar. On November 28 120 units of globin insulin and 55 units of regular insulin were administered and at 4:30 P.M. he was sugar-free for the first time and his blood sugar was 135 mg. per 100 cc. On the following day he was sugar-free but on November 30 he began to run a temperature, and from then until December 11 he was uncontrolled, though he received as much as 200 units of globin insulin and 60 units of regular. However, since December 11 his control has gradually returned on 200 units of globin insulin and 60 of regular insulin, so that on the day of discharge, December 27, his blood sugars at 11:30 and 4:30 were 116 and 114 mg. per 100 cc., respectively, and he was sugar-free. At the present time (February 8, 1940) he is taking 20 units of regular insulin and 200 units of globin insulin each morning with absence of sugar in all specimens.

TABLE 1.—DATA OF CASE 1.

Date, 1939.	Insulin.	Units.	Urine sugars.	Blood sugars.
11/27 . . . .	Protamine	120	6 A.M.—++++	Fasting—224
	Regular	90	11 A.M.—++++	
			1 P.M.—++++	
			7 P.M.—+++	
			9 P.M.—+++	
11/29 . . . .	Globin	120	6 A.M.—0	11:30 A.M.—158
			11 A.M.—0	4:30 P.M.—166
1940.			9 P.M.—0	
2/8 . . . .	Globin	200	6 A.M.—0	
	Regular	20	11 A.M.—0	
			9 P.M.—0	

TABLE 2.—DATA OF CASE 2.

Date, 1939.	Insulin.	Units.	Urine sugars.
10/26 . . . .	Protamine	98	6-11 A.M.—++++ 11-5 P.M.—++++ 5-9 P.M.—++++ 9-6 A.M.—++++
10/27 . . . .	Protamine	98	6-11 A.M.—++++ 11-5 P.M.—++++ 5-9 P.M.—++++ 9-6 A.M.—++++
10/28 . . . .	Globin	80	6-11 A.M.—0 11-5 P.M.—0 5-9 P.M.—0 9-6 A.M.—0
10/29 . . . .	Globin	75	6-11 A.M.—0 11-5 P.M.—0 5-9 P.M.—+ 9-6 A.M.—0
10/30 . . . .	Globin	75	6-11 A.M.—0 11-5 P.M.—0 5-9 P.M.—0 9-6 A.M.—0
Diet, 300-100-180.			

CASE 2 (No. 588526).—A man, aged 20, was admitted in acidosis on September 10 with a  $\text{CO}_2$  of 12, and discharged on November 1, 1939. During this time he received 200 carbohydrate, 70 protein, and 100 fat daily. Later this was increased to 300 carbohydrate, and from October 4 until his discharge he received 300 carbohydrate, 100 protein and 180 fat. He was unregulated on 98 units of protamine insulin until October 28. On the 28th he received 80 units of globin insulin, and this was gradually decreased during the next 3 days to 73 units with almost complete clearing up of his glycosuria.

CASE 3 (No. 595600).—An unmarried man, colored, aged 35, has had diabetes since 1934. He came in for acidosis which responded to the usual method of treatment and then was placed on a diet of 250 carbohydrate,

TABLE 3.—DATA OF CASE 3.

Date, 1939.	Insulin.	Units.	Urine sugars.	Diet.		
				C.	P.	F.
12/18 . . .	Protamine	82	6-11 A.M.— +	250	70	100
			11-5 P.M.— + + + +			
			5-9 P.M.— + + + +			
			9-6 A.M.— + + + +			
12/19 . . .	Protamine Standard	82 15	6-11 A.M.— + + + +	300	70	100
			11-5 P.M.— + + + +			
			5-9 P.M.— + + + +			
			9-6 A.M.— + + + +			
12/28 . . .	Globin	70	6-11 A.M.— + +	300	70	100
			11-5 P.M.— 0			
			5-9 P.M.— +			
			9-6 A.M.— 0			
12/29 . . .	Globin	72	6-11 A.M.— 0			
			11-5 P.M.— 0			
			5-9 P.M.— 0			
			9-6 A.M.— 0			

TABLE 4.—DATA OF CASE 4.

Date, 1940.	Insulin.	Units.	Urine sugar.	Blood sugar.	Diet.		
					C.	P.	F.
1/17	Protamine	60	6-11 A.M.— +		200	70	100
			11-5 P.M.— +				
			5-9 P.M.— + +				
			9-6 A.M.— 0				
1/18	Protamine	60	6-11 A.M.— +				
			11-5 P.M.— + +				
			5-9 P.M.— + +				
			9-6 A.M.— + + +				
1/19	Protamine	60	6-11 A.M.— +				
			11-5 P.M.— 0				
			5-9 P.M.— +				
			9-6 A.M.— +				
1/30	Globin	35	6-11 A.M.— +		250	70	100
			11-5 P.M.— 0				
			5-9 P.M.— +				
			9-6 P.M.— +				
1/31	Globin	30	6-11 A.M.— +				
			11-5 P.M.— 0				
			5-9 P.M.— +				
			9-6 A.M.— +				
2/1	Globin	30	6-11 A.M.— 0	11:30—85 4:30—60			
			11-5 P.M.— 0				
			5-9 P.M.— 0				
			9-6 A.M.— 0				

70 protein and 100 fat daily, and was given protamine insulin with standard insulin, in amounts up to 82 units of protamine and 60 units of standard insulin without any effect on the glycosuria. This period lasted 10 days. He then was given a single dose of 80 units of globin insulin. This was followed by an immediate clearing up of his sugar and the occurrence of insulin shocks. The insulin was finally reduced to 72 units a day, and all specimens became sugar-free.

CASE 4 (No. 581009).—A colored laundress of 58 with marked hypertension. Diabetic symptoms came rather suddenly about 7 months ago. She was tried on protamine insulin up to 60 units a day for about a week with fair regulation, then shifted to 60 units of globin insulin, with marked improvement. Having abnormally low blood sugars and symptoms of insulin shock, it was apparent that she required considerably less globin insulin. The dose was reduced by half, and the diet increased from 200-70-100 to 250-90-100. Now she requires 30 units of globin insulin to make her sugar-free most of the time.

The following is a table of the sugar excretion for about 1 month of a diabetic boy of 16 (No. 583702) who has been on globin insulin since May, 1938. At present he receives a single dose of 94 units each morning.

TABLE 5.—DATA ON CASE NO. 583702. URINE SUGAR DETERMINATIONS.

Date, 1940.	12 M. to 8 A.M.	8 A.M. to 12 N.	12 N. to 4 P.M.	4 P.M. to 8 P.M.	8 P.M. to 12 M.	Remarks.
2/1	0	0	0	0	0	
2/2	0	0	0	0	0	
2/3	0	+	++	0	0	
2/4	+	+	0	0	0	
2/5	0	0	0	0	0	Very weak—2 lumps sugar
2/6	0	0	0	0	+	
2/7	+	+	0	0	0	
2/8	+	+	0	0	0	
2/9	0	0	0	0	0	
2/10	0	0	0	+	+	
2/11	0	0	0	0	0	Felt weak
2/12	0	++	+	+	+	
2/13	0	0	0	0	0	
2/14	0	0	++	+++	+++	Shocked
2/15	0	0	0	0	0	
2/16	0	+	0	0	0	
2/17	0	0	+	0	0	
2/18	0	+	0	+	0	
2/19	0	0	0	0	0	
2/20	0	0	+	+	0	
2/21	+	+	0	0	0	
2/22	0	0	0	0	0	
2/23	0	+	0	0	0	
2/24	0	0	+	0	+	
2/25	0	0	0	0	0	
2/26	0	+	0	0	0	
2/27	0	0	+	0	0	
2/28	0	0	0	0	0	
2/29	0	0	0	0	0	
3/1	0	+	0	+	0	
3/2	0	0	0	0	0	
3/3	0	0	0	0	0	
3/4	+	0	0	0	+	

The following table summarizes our experience with globin insulin:

TABLE 6.—PATIENTS RECEIVING GLOBIN INSULIN TO MARCH, 1940.

History No.	No. of units.		No. of months on globin insulin.	Diet.			Urine sugar last visit.				Blood sugar last visit, 11:30 A.M.
	Initial.	Present.		C.	P.	F.	Fasting.	11:30.	4:30.	10:00.	
457353	50	46	20	200	70	100	++++				147*
581009	60	30	2	250	90	100	0	0	0	0	75
457988	80	74	4	150	60	90	++++	+++	+	++	144
245926	88	72	28	140	80	80	+	+	0	0	183
71851	80	75	21	310	70	100	+	0			83
354588	70	64	27	175	70	75	0	0	0	0	90
241966	100	48	15	200	80	90	0	0	0	0	
51008	45†	55†	16	175	90	120	+	0			301*
	10§	15§									
567272	50	36	14	200	80	100	0	0	0	0	85
309995	85	75	11	250	80	80	+				74
356561	35	40	24	200	90	150					
545439	70	40	18	170	80	120	0	0	0	0	
463000	55	65	4	230	80	100	+++	++++	+++	++++	150
68476	54	50	21	225	70	100	0	+	0		
245481	80	65	24	150	80	75	0	0	0	0	153
533702	48	90	21	250	120	150	+	+	0	0	64*
327875	110	126	15	300	110	130	0	0	0	0	172
389730	60	40	16	290	90	90	0	0	0	0	244

\* Blood sugar taken at 4:30 P.M.

† Has severe cold.

‡ Globin insulin.

§ Standard insulin.

**Discussion.** The cases presented above show striking improvement in some instances when they are transferred from protamine zinc insulin to globin insulin. Although such improvement may be seen in the course of any insulin therapy, the marked change noted on shifting to globin insulin seems to be more than merely coincidental.

It is also to be noted that the insulin requirement of patients using globin insulin over a long period decreases in the majority of cases.

It is of interest to note that although some of these cases have received globin insulin daily for over 2 years, no case of allergy has developed. Moreover, several patients who had severe skin reactions after injections of protamine zinc insulin, such as redness, urticaria and infiltration, were promptly relieved of this condition when changed to globin insulin.

Thanks are due to the Burroughs Wellcome & Co. Experimental Research Laboratories, who kindly furnished the globin insulin, and to Drs. Edgar Stillman and Bertram Sanger for their coöperation, and to Miss Ruth Husing for the laboratory work.

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## LEVULOSURIA.

## A STUDY OF TWO CASES IN BROTHERS.

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BIOLOGIC anomalies include certain metabolic functional disorders which are detected by chemical examination of body fluids. The many types of sugars taken in the human food offer possibilities for the occurrence of instances of partial or absolute inability of the organism to metabolize any one of them. Aberrations of dextrose metabolism occurring in the young may be accompanied by changes in the number or cell structure of the islets of Langerhans of the pancreas. Pentose and levulose (fructose) have been recognized in the urine of persons who have no definite signs of disease, but who display a remarkable defect in their lack of ability to convert either of these sugars into glycogen.

Levulose, a levorotatory monosaccharide, is present in considerable amount in fruits and honey, and is formed in the break-up of cane sugar. It reduces Benedict's and Fehling's solutions, behaving like dextrose in this respect except that reduction proceeds in the cold as well as with heat. It forms a brown precipitate with hydrochloric acid and resorcinol (Seliwanoff's test). Its osazone crystals are characteristic and have a constant melting point. With these means of identification, levulosuria is being detected more frequently, although only 31 cases have appeared in the literature.

Two cases of levulosuria in brothers have recently come under my observation.

CASE 1.—A Jewish boy of 14, at birth weighed 5 pounds and was a full term child. Sugar was said to have been found in his urine at  $2\frac{1}{2}$  years when his tonsils and adenoids were removed. His diet had been restricted more or less since, and there were episodes every 2 to 3 months of vomiting and occasionally "air hunger." He had been under the care of 12 doctors at different times with a diagnosis of diabetes mellitus. He had had insulin on two occasions for short periods. Nothing is known about the blood sugar levels except 8 years ago when he was in the Albany Hospital for observation. Normal figures were observed at the same time that mellituria was present. For the past 10 years under restricted diet his weight has been subnormal. In June, 1938, his weight was 92 pounds, on July 30, 1938, 86½ pounds. He tired easily and spent most of his time sitting and reading. However, he was an excellent student and led his class in school.

Two days previous to my first seeing him (July 30, 1938), he had a severe vomiting spell and in a 6-day period had lost 6 pounds. His mother assumed that his diabetes was out of control, although carbohydrates had been much restricted for several years. There had never been any excessive hunger, thirst, or polyuria.

*Physical Examination.* An underweight boy, 61½ inches tall, weight 83½ pounds. The heart showed a loud systolic murmur at mitral and aortic areas, transmitted slightly into the neck, but with no thrill. Second aortic

and pulmonic sounds somewhat snapping in character. The examination otherwise disclosed nothing abnormal.

*Laboratory Examination.* Hemoglobin, 86%; blood pressure, 134/90; pulse, 84, regular. Urine: pale; specific gravity, 1.005; sugar, ++; albumin, slight trace. Sediment, negative. Blood sugar at 3 p.m., 154 mg.

Blood Wassermann reaction was negative.

He was admitted to the Samaritan Hospital, July 31, 1938, for investigation of his mellituria. While in the hospital he was given an 1800 cal. diet: C-130; P-75; F-98, and insulin u10-u10-u10. Later this was changed to u20 of protamine zinc insulin. The mellituria continued, and gradually the insulin was increased to u45 and the diet changed to C-142; P-75; F-85, with little effect on the urine sugar. The blood sugar at the hospital the morning after admission was 95 mg. per 100 cc. and 4 days later it was 85 mg. per 100 cc. with the urines at these times being positive for sugar. No acetone or diacetic acid was ever found. It was suspected that the case was not diabetes, but mellituria of another nature. Several different urine specimens were examined by the Seliwanoff test for fructose, and found positive. The phenylhydrazine test showed crystals of glucose or fructose present, but none of other sugars. The sugar was fermented by yeast. A specimen of urine submitted to Prof. Arthur Bray of Rensselaer Polytechnic Institute and others examined by Prof. Arthur Knudson of Albany Medical College were found to rotate polarized light to the left.

Further studies were made from time to time, the mellituria persisting.

September 22, 1938, 24-hour specimen of urine: acid reaction; on a diet devoid of fruits or cane sugar, contained no sugar.

October 7, 1938, basal metabolic rate + 13%. Weight 94½ pounds.

November 2, 1938, he felt very well. Urine sugar + + +. Mitral murmur had disappeared. P<sub>2</sub> accentuated only slightly.

December 3, 1938, weight 101½ pounds. Blood pressure 112/58; pulse 90. Systolic murmur at mitral area, not transmitted.

October 15, 1938, dextrose tolerance test showed a normal curve.

October 20, 1938, fructose tolerance test using 56 gm.

BLOOD SUGAR		Mg. per 100 cc.
Fasting		84
30 min. after 56 gm. of fructose		109
2 hrs. after 56 gm. of fructose		125
3 hrs. after 56 gm. of fructose		117
URINE SUGAR (at the above periods):		Output (cc.)
Fasting		0.0
30 min. after 56 gm. of fructose		44
1 hr. after 56 gm. of fructose		24
2 hrs. after 56 gm. of fructose		48
3 hrs. after 56 gm. of fructose		40
		156
		4.0

During 1939 his weight increased to 112 pounds. He now feels normal in every way. The mitral murmur has disappeared. The mellituria has persisted. The urine before breakfast is negative to Benedict's test, or contains only a trace of sugar. The sugar reduces Benedict's solution in the cold as well as with heat. During the day it is constantly present. A small amount of fruit is consumed, but so far there have been no apparent unfavorable symptoms.

His weight on February 21, 1940, was 119½ pounds, a total gain of 33 pounds since July 30, 1938. Height had increased 1½ inches. Blood pres-

sure 112 to 120 systolic, 60 to 65 diastolic. Pulse 66 to 90. A systolic murmur was heard occasionally at apex and base. Occasionally the urine contained a faint trace of albumin, but no renal elements in the sediment. Urea clearance test normal.

On February 20, 1940, using Roe's method for blood levulose the following determinations were made 2 hours after lunch:

Blood Dextrose.	Blood Levulose.	Urine Dextrose.	Urine Levulose.
96.1 mg.	7.5 mg.	3+	3+

On the basis of the above findings, the patient was advised to eat generously and get his weight and strength back as much as possible. He and his parents were rather skeptical of this advice after so many doctors had told him he had diabetes and to beware of starches and sugars. Nevertheless, with only a slight restriction of fruits he followed this régime and his weight and strength returned rapidly. He graduated a year later from Intermediate School leading his class in scholarship and taking part in many physical activities he had formerly been denied.

CASE 2.—The familial history of Case 1 revealed that the mother and father were living and well, although of a very nervous type. One brother died of tuberculosis following whooping cough at the age of 30. Another brother, aged 20, had been suspected recently of having sugar in his urine and the following is his story.

He is the next oldest brother to Case 1, rather shy, highly nervous, and plays the violin in a symphony orchestra. He had been attending a boy's camp for 2 months and was losing weight steadily because his physician had told him he had "sugar diabetes," and carbohydrates were removed almost entirely from his diet. His maximum weight had been 140 pounds, 3 months previously. This had dropped to 115 pounds. For several months there had been furuncles on his arms, but these had recently healed.

At the age of 10 a school physician is said to have noted a murmur in his heart. In high school his pulse rate was frequently around 95. He finished high school in 1937. There is no history of rheumatic fever, scarlet fever, pneumonia or typhoid, or other serious illness. His habits are good. He takes no exercise in addition to his work which is largely clerical, or delivering dry goods in an automobile. His only other complaint is a rather excessive shyness and frequent palpitation of the heart. There has never been excessive thirst, hunger, pruritus, or urinary frequency.

On physical examination his height was 5 feet 10 inches; weight 115 pounds, average normal 152 pounds. The reflexes were hyperactive. His heart showed a blowing systolic murmur, loudest at the mitral and aortic areas, transmitted into the axilla, but not into the neck. No thrill could be detected.  $P_2$  was not accentuated. The pulse rate in my office was 110 to 120, and regular. Blood pressure was 178/70. Blood Wassermann reaction was negative.

The postprandial urine gave a 3+ reaction for sugar, and 1+ for albumin. The sediment showed a moderate number of hyaline and granular casts and a few leukocytes. The sugar in the urine was fermented by yeast, and reduced Benedict's reagent in the cold as well as with heat. Seliwanoff's and Boucharde's tests were positive and the osazone test was positive for glucose or levulose (the crystals are similar). Urine specimens rotated polarized light to the left.

A dextrose tolerance test gave the following result:

	Blood sugar.	Urine sugar.
Fasting	95	Negative
30 min. after 100 gm. glucose	135	Negative
60 min. after 100 gm. glucose	157	Negative
150 min. after 100 gm. glucose	75	Negative

On a diet of C-180; P-75; F-95; glycosuria was pronounced. Five units of protamine zinc insulin did not affect the condition, nor did 20 units daily. The urine remained constantly negative just before meals and strongly positive for sugar after meals. He omitted insulin for 2 days, ate anything he wished and then showed a normal dextrose tolerance test. On a general diet he gained 5 pounds in 12 days, during which time the blood sugar remained within normal limits, the highest figure 116 mg. per 100 cc. In 24 hours an output of 2 quarts of urine contained 5.5 gm. of sugar.

The blood pressure was always elevated, varying from 152 to 184 systolic, 50 to 70 diastolic. The pulse rate was 110 to 140. The dextrose tolerance test on October 15, 1938, was normal. A levulose tolerance test gave the following results:

BLOOD SUGAR	Mg. per 100 cc.
Fasting . . . . .	80.0
30 min. after taking 56 gm. of levulose . . . . .	106.0
1 hour after taking 56 gm. of levulose . . . . .	107.0
2 hours after taking 56 gm. of levulose . . . . .	133.3
3 hours after taking 56 gm. of levulose . . . . .	129.0

#### URINE SPECIMENS (at the above periods):

Fasting: Acetone and diacetic acid, 0; Sugar, 0.

	Specific gravity.	Output cc.	Sugar gm.
30 min. . . . .	1.017	65	.34
1 hr. . . . .	1.015	63	1.05
2 hr. . . . .	1.024	90	3.15
3 hr. . . . .	1.028	110	3.30
Total		328	7.84

The basal metabolism was +12%. He always showed tachycardia in the presence of his physician, but insisted his pulse rate and nervousness were much less when elsewhere than in a doctor's office. There was a loud systolic murmur at the apex. Numerous urine tests in addition to sugar revealed a trace of albumin and hyaline casts, a few granular casts and a few leukocytes. Urea clearance test was normal.

An electrocardiogram showed right axis deviation and sinus tachycardia.

Between September 10, 1938, and February, 1940, on a general diet, with no restrictions except for no excess of fruits and honey, his weight increased from 117½ pounds to 134½ pounds. He now feels strong, works steadily, and looks in the best of health in contrast to the thin, rather emaciated physique of 2 years ago.

On February 6, 1940, using Roe's method for blood levulose, the following determinations were made:

	Blood Dextrose mg. per 100 cc.	Blood Levulose mg. per 100 cc.	Urine Dextrose.	Urine Levulose.
Fasting . . . . .	101	0.0	0	0
2 hr. after noon meal	98	5.6	3+	3+

**Discussion.** The data above given seem sufficient to justify the opinion that we are dealing with true levulosuria occurring in Jewish brothers and probably existing since early childhood. The error made by various physicians of regarding the mellituria as glycosuria and the disease as "diabetes mellitus" has doubtless been made many times. While only 31 cases are found in the literature, there are probably many unrecorded although recognized instances of this



interesting metabolic anomaly. In Joslin's clinic it is considered a rare condition. Root<sup>5</sup> writes, "We only find a very occasional case, although we test every patient with glycosuria for levulose now."

The levulosuria when undetected may be a very serious matter to the patient because of the dietary restrictions naturally adopted in the attempt at controlling the mellituria, since it is uninfluenced by insulin. My 2 cases were rapidly being reduced to a state of emaciation by carbohydrate withdrawal. A diet of generous proportions when prescribed was viewed by them and their parents with much misgiving and even alarm, after the years of diabetic discipline to which they had been subjected. Their response to adequate food was dramatic and serves to emphasize the prime importance of the blood sugar level as the basic guide in diabetic diagnosis.

These 2 cases occurring in young brothers makes it likely that there is a congenital factor involved, of relative inability to metabolize levulose, or to retain it in the blood stream long enough to be broken down and used.

The tolerance for levulose is said to be less in persons with impaired liver function, and a levulose test for liver disease is based on this idea. In the cases here reported there is nothing to suggest hepatic derangement, except this one finding of levulose in large quantities in the urine. The levulose tolerance test demonstrates adequate liver function based on the blood concentration of the sugar.

The method devised by Roe<sup>4</sup> for differentiating quantitatively levulose from dextrose in the blood was applied to the urine of these 2 patients. While exact weights were not determined, it was found that at the time the levulose was present in large amount in the urine (3+) an approximately equal amount of dextrose was being passed, and at a time when the total blood sugar was within normal limits. The urines were levorotatory, but this is to be expected since the levorotatory power of levulose is twice that of the dextro-power of dextrose. The latter sugar then might go unrecognized in the presence of an equal amount of levulose.

A possible explanation of the glycosuria occurring only at the same time as the levulosuria is that the kidneys permit dextrose to escape in about equal amount with the levulose, since they have the same molecular weights. In Case 2, with signs of renal irritation and arterial hypertension, the kidneys might be suspected of being more permeable to sugar than normal. Case 1, however, shows no evidence of kidney disease. Since the boys are brothers, an inherited factor is probably the basic one, although the renal element in Case 2 must be considered as possibly affecting the quantitative results, but in which direction can only be conjectured. It seems unlikely that we are dealing here with "familial-nephritic levulose diabetes."

The output of levulose in 3 hours following the ingestion of 56 gm., was 7.1% for Case 1 without renal complications, and 14% for Case 2 with hypertension and cylindruria. Fourteen per cent in

3 hours is approximately the amount noted by Silver and Reiner,<sup>6</sup> and Marble and Smith.<sup>3</sup>

The polariscope was first used in urinalysis by Biot in 1840, but von Gorup-Besanez<sup>7</sup> was the first to note a levorotatory sugar that behaved like fructose. Silver and Reiner<sup>6</sup> in 1934 found 27 cases of levulosuria reported since 1876 and added 3 of their own. They noted only 1 case of essential levulosuria in the American literature since 1912.

Following the thorough studies of Silver and Reiner, Marble and Smith in 1936 reported the one case they had found, after examining 136 consecutive specimens of urine containing sugar, a 17-year-old girl who had fructosuria with mild diabetes. All of these cases, including those of Silver and Reiner and mine, were in young people—22 years the oldest. Five cases were Jewish, and 2 of Silver and Reiner's were in Italian-born brothers.

Levulose has been found to protect slightly against the hypoglycemia of hyperinsulinism, but an analysis of the blood sugar curves in the cases reported show that in persons with levulosuria uncomplicated by diabetes mellitus the amount of levulose retained in the blood is probably so small as to be of little importance in "doubling" for dextrose.

The younger of the 2 patients may be suspected of having an old rheumatic valvular heart disease of very mild degree, not sufficient to cause any clinical cardiac disturbance, or the mitral murmur might be explained on a so-called functional basis.

The older brother, however, offers a complication which, were he the only case studied, would possibly carry much weight in explaining the urinary sugar. There is no history of rheumatic fever or scarlet fever, but he is an excellent example of paroxysmal tachycardia with hypertension. The electrocardiogram shows right axis deviation. In addition, he has albuminuria and frequently hyaline and granular casts in his urine. The blood nitrogen has always been normal, as have urea clearance tests. Nevertheless, there may be an element of increased renal permeability due to a mild degree of chronic nephritis.

The incidence of glycosuria in paroxysmal hypertension is worth discussing briefly. Labbé, Tinel, and Doumer<sup>2</sup> report a case of glycosuria associated with episodes of systolic pressure as high as 280 mg. Hg. Foucar<sup>1</sup> regards the transient glycosuria during or immediately after periods of paroxysmal hypertension as strictly renal in type, "due to the sudden increase in pressure in the 'arterial mirabile' of the kidney (glomerular tufts of the renal corpuseles, including the afferent and efferent glomerular arterioles)." He found in the literature 12 cases, in which transient glycosuria was noted only in 3, and the highest blood sugar 125 mg. per 100 cc. Most of the cases had tumors of the adrenal gland, usually pheochromocytomas or paragangliomas. In Case 2 of the writer's, the pulse rate would reach 140 per minute and the systolic blood pressure 180 mg. Hg. Any moderate nervous strain in addition to visiting a physi-

cian's office probably produced the same reaction. It is possible that he harbors a pheochromatocytoma, but only time will throw further light on this possibility.

The great production of epinephrine by these tumors carries with it the possibility of its being liberated into the blood stream during emotional stress, or even by postural changes which might aid in expressing epinephrine from it. This sudden liberation of epinephrine produces an effect on the liver cells resulting in a rapid discharge of glycogen with resulting hyperglycemia and glycosuria. While Case 2 did not show hyperglycemia, the circumstances, including as they do paroxysmal hypertension, warrant a consideration of all facts involving sympathetic stimulation and glycogen mobilization.

Levulosuria, then, as illustrated by these 2 cases in young brothers, is probably an expression of congenital permeability of the kidneys to levulose, and based on no known anatomical lesion of the kidney, or of the liver. The occurrence of dextrose in the urine along with levulose is probably analogous to the leakage of levulose through the kidneys in reported cases of severe glycosuria in diabetes mellitus and based on purely physical factors of altered glomerular filtration.

**Summary.** Two cases are reported of so-called essential levulosuria in young Jewish brothers. They bring the total on record to 33. The condition appears to be a metabolic anomaly in which the organism exhibits a partial or complete inability to convert levulose into glycogen. This seems to be due not to a hepatic deficiency, but to increased permeability of the kidneys by the levulose molecule. This renal hypothesis does not postulate any inherent kidney disease, although in one case with paroxysmal hypertension there were signs of renal irritation. In both cases an approximately equal amount of glucose was excreted, but only at the same time that levulose was passing through the kidneys. Normal dextrose and levulose tolerance tests were obtained.

The clinical importance of the condition lies in its early recognition, before the patient is subjected to the rigors of a diabetic regimen which may severely handicap the growing child. The treatment is reassurance that he does not have diabetes mellitus, and a diet without special restrictions. So far as is known, the passage of levulose through the kidneys causes no harm, although continual observation of these interesting people throughout their lives may later alter this dictum in some degree.

The writer wishes to thank Dr. Stewart H. Jones for his assistance in the early study and diagnosis of these cases, and Miss Helen Lutz of the Cluett Pathological Laboratory, Samaritan Hospital, for her technical help.

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## STUDIES ON THE PRESERVATION OF HUMAN BLOOD.

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IN the United States human blood is commonly preserved in "banks" for transfusion by the addition of 14 cc. of a sterile 2.5% solution of chemically pure sodium citrate in physiologic saline solution to each 100 cc. of blood, giving a 0.35% concentration of sodium citrate with preservation at 4° to 6° C. in a refrigerator. Most attention has been given the matter of preservation of erythrocytes and the prevention of hemolysis but as I pointed out in 1939,<sup>8</sup> blood so preserved showed such rapid disintegration of neutrophils with reduction in their phagocytic activity, along with rapid disintegration of platelets and gradual loss in bactericidal activity, that preserved citrated blood was considered inadvisable for the treatment of the anemias, hemorrhagic states and infections although apparently useful in the treatment of acute hemorrhage and surgical shock.

Recently there has been an increasing appreciation of the fact that if dextrose or dextrin is added to preserved citrated blood, sodium penetration and cell swelling are decreased with inhibition of hemolysis as originally shown by Rous and Turner.<sup>14</sup> Thus Maizels and Whittaker<sup>10b,c</sup> have reported not only these effects following the addition of carbohydrates but also an increase of surface area of the erythrocytes so that they can tolerate a larger absolute inflow of fluid. Aylward and his colleagues<sup>1</sup> have also found that citrate-glucose preservation is not only superior to citrate alone in delaying hemolysis but that it also retards chemical changes in the cells leading to an increase of plasma inorganic phosphate with reduced plasma potassium, probably due to a lower degree of hemolysis. DeGowin, Harris and Plass<sup>5a</sup> have likewise found that large amounts of isotonic dextrose not only reduce hemolysis but that the erythrocytes better resist the effects of shaking and agitation. Whether or not efforts toward the prevention of hemolysis in preserved blood are a matter of practical importance, although desirable from the standpoint of therapy, cannot be stated and particularly since O'Shaughnessy and his colleagues<sup>11</sup> have reported that 5% solutions of hemoglobin in Ringer's solution are capable of carrying oxygen and maintaining osmotic pressure although not capable of maintaining life more than 36 hours because of rapid removal by the cells of the reticulo-endothelial system.

Belk, Henry and Rosenstein<sup>2</sup> have confirmed my observations on the marked and rapid disintegration of granulocytes and platelets in preserved citrated blood as well as showing increased fragility of the erythrocytes, rapid glycolysis, changes in oxygen capacity and plasma carbon dioxide. They also observed that the transfusion of hemolyzed blood produced jaundice in some cases but whether or not preservation with dextrin or dextrose with sodium citrate results in better preservation of granulocytes, platelets and the immunologic properties of plasma has not been determined.

**Purpose of Investigation.** Under the circumstances I have thought it advisable to determine the properties of four well-known preservatives (two without and two with carbohydrate) not only in relation to the fragility, dehemoglobinization and disintegration of erythrocytes, but likewise in relation to the preservation of leukocytes with special reference to the neutrophils and platelets as well as of prothrombin time, isoagglutinins, complement and bactericidal activity. Some attention has been given prothrombin as based upon examinations employing the method of Howell but the technique employed for the collection and preservation of blood did not permit the use of the method of Quick. Nor have I included determinations for potassium since DeGowin and his colleagues<sup>5b</sup> have shown that there is progressive diffusion from human erythrocytes into plasma reaching the maximum in from 15 to 20 days and because variations in sodium, chloride, citrate and dextrose in preservatives as well as different temperatures and atmospheres did not affect the rate of diffusion which cannot be explained by the release of this ion from completely hemolyzed corpuscles. Furthermore, in blood preserved for as long as 30 days it was found that the diffused potassium was not toxic nor high enough to cause significant changes in the serum potassium of the recipient.<sup>4</sup>

**Methods.** Two adult donors were selected belonging to Groups A and B and the blood of each used with the following four preservatives:

(a) *Sodium Citrate* (citrate):

Sodium citrate (dihydric) . . . . .	2.5 gm.
Distilled water . . . . .	100.0 cc.

12.6 cc. of the solution was used with 90 cc. of blood giving a final concentration of 0.35% citrate.

(b) *Moscow Institute of Hematology* (M.I.H.) as given by Elliott:<sup>6</sup>

Sodium chloride . . . . .	3.5 gm.
Sodium citrate (dihydric) . . . . .	2.5 "
Potassium chloride . . . . .	0.1 "
Magnesium sulphate . . . . .	0.002 "
Distilled water . . . . .	500.0 cc.

50 cc. of the solution was used with 50 cc. of blood.

(c) *Modified Rous-Turner* (R-T) as described by DeGowin, Harris and Plass:<sup>5a</sup>

Solution A: 3.2 gm. sodium citrate (dihydric) dissolved in 100 cc. of distilled water.

Solution B: 10.8 gm. dextrose dissolved in 200 cc. of distilled water.

For use 10 cc. of Solution A and 65 cc. of Solution B were mixed with 50 cc. of blood.

(d) *Maizels and Whittaker* (M-W) as described by these authors:<sup>10a</sup>

Sodium chloride . . . . .	0.43 gm.
Sodium citrate (dihydric) . . . . .	1.05 "
Dextrin . . . . .	8.5 "
Distilled water . . . . .	100.0 cc.

For use 40 cc. of the solution was mixed with 80 cc. of blood.

Before use each preservative solution was sterilized in the Arnold sterilizer for 1 hour on each of 2 days in succession and all examined for sterility by aerobic and anaerobic cultures.

The mixtures of blood and preservative were kept in a refrigerator at 4° to 6° C. and the following 10 examinations conducted with each within 24 hours, 3, 5, 7, 10, 14 and 21 days after collection:

1. Macroscopic record of spontaneous dehemoglobinization.
2. Fragility or tonicity of erythrocytes.
3. Total erythrocyte counts.
4. Total leukocyte counts and morphologic changes in the neutrophils.
5. Differential leukocyte counts.
6. Platelet counts by the smear method.
7. Prothrombin time of the plasma (Howell method).
8. Preservation of isoagglutinins in the plasma.
9. Complement content of the plasma for sensitized sheep corpuscles.
10. Bactericidal activity of the plasma for *B. typhosus*.

**Results.** *Spontaneous Dehemoglobinization of Erythrocytes.* As shown in Table 1, spontaneous dehemoglobinization occurred in very much less degree over the period of 21 days in the case of the two carbohydrate-citrate preservatives than in the two without dextrose or dextrin; of the latter dextrose (modified Rous-Turner) was slightly better than dextrin (Maizels and Whittaker) in the preservation of the erythrocyte against dehemoglobinization. I use this term instead of "spontaneous hemolysis" because, as will be shortly shown in Table 4, the presence of dissolved hemoglobin in the plasma does not appear to be due entirely to hemolysis of the erythrocytes.

TABLE 1.—SPONTANEOUS DEHEMOGLOBINIZATION OF ERYTHROCYTES IN PRESERVED BLOODS KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	0*	0	0	0	0	0	0	0
3	2	2	0	0	0	0	0	0
5	3	3	2	1	0	0	0	0
7	4	3	3	2	0	0	0	0
10	4	3	3	2	0	0	1	0
14	4	4	3	3	0	0	1	1
21	4	4	3	3	0	0	1	1

\* 0 = no macroscopic discoloration; 1 = very slight discoloration; 2 = slight discoloration, etc.

*Fragility or Tonicity of Preserved Erythrocytes.* In conducting these tests a portion of each preserved blood was centrifuged and the corpuscles suspended in an equal volume of physiologic saline solution (50% suspension). One drop was added to 1.25 cc. of solutions of sodium chloride in water varying from 0.28 to 0.5% in small test tubes and the mixtures allowed to stand at room temperature for 2 hours when the readings for initial and complete hemolysis were made.

*Initial hemolysis* of fresh blood commonly occurs at 0.42 to 0.44% sodium chloride in the method employed and as shown in Table 2 all of the preservatives showed a slight increase of fragility at the end of 3 days' preservation (0.5% sodium chloride) which kept quite constant to 21 days.

TABLE 2.—FRAGILITY OF ERYTHROCYTES (INITIAL HEMOLYSIS) IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	0.46	0.46	0.46	0.46	0.46	0.46	0.46	0.46
3	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
7	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
10	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
14	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
21	0.5	0.5	0.5	0.5	0.48	0.48	0.5	0.5

*Complete hemolysis* of fresh blood commonly occurs at 0.32 to 0.36% sodium chloride in the method employed and, as shown in Table 3, tonicity was fairly well preserved by all four preservatives for the period of 21 days but somewhat better by the two carrying dextrose (R-T) and dextrin (M-W) than the two without carbohydrate (citrate and M.I.H.). It would appear, therefore, that dextrose and dextrin in preservatives tend to protect the tonicity of erythrocytes.

TABLE 3.—FRAGILITY OF ERYTHROCYTES (COMPLETE HEMOLYSIS) IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	0.38	0.36	0.34	0.36	0.38	0.38	0.36	0.36
3	0.38	0.38	0.38	0.38	0.38	0.38	0.38	0.38
5	0.36	0.38	0.38	0.38	0.38	0.38	0.38	0.38
7	0.36	0.40	0.38	0.38	0.36	0.36	0.38	0.38
10	0.38	0.40	0.38	0.38	0.38	0.38	0.38	0.38
14	0.40	0.40	0.40	0.40	0.38	0.38	0.38	0.38
21	0.44	0.46	0.44	0.42	0.38	0.36	0.36	0.42

*Preservation of Erythrocytes.* The results of total erythrocyte counts shown in Table 4 were made after gentle but thorough shaking of the mixtures. In this connection the dilution factor

TABLE 4.—PRESERVATION OF ERYTHROCYTES IN BLOOD KEPT AT 4° TO 6° C.  
(Erythrocytes given in millions per c.mm.)

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	4.96*	4.92	3.27	3.15	2.85	2.15	3.75	3.64
3	4.85	4.98	2.81	2.99	2.75	2.38	3.70	3.68
5	4.68	4.85	2.80	2.85	2.29	2.09	3.63	3.50
7	4.51	4.61	2.71	2.50	2.04	2.10	3.50	3.40
10	4.29	4.33	2.60	2.40	2.32	2.19	3.37	3.46
14	4.32	4.24	2.51	2.50	2.28	2.21	3.37	3.39
21	4.16	4.07	1.83	1.75	2.26	2.15	3.43	3.46

\* Per c.mm. of blood-preservative mixture.

from the volume of preservative in relation to volume of blood must be kept in mind but by reading the figures downward in the table the total erythrocyte counts may be compared at the different intervals of preservation.

Allowing for experimental error in making the counts it appears that the two carbohydrate preservatives (R-T and M-W) showed the least reduction over the period of 21 days, although closely similar results were observed with the plain citrate preservative while the M.I.H. preservative showed the poorest preservation of the four methods employed. When compared with Table 1, however, it is noted that the plain citrate preservative showed the highest degree of dehemoglobinization as judged by the discoloration of plasma, but apparently this was not entirely due to hemolysis of the erythrocytes but largely to diffusion of hemoglobin.

*Preservation of Leukocytes.* The results of total leukocyte counts made after gentle but thorough shaking of the mixtures are shown in Table 5. In this connection the dilution factor from the volume of preservative in relation to volume of blood must likewise be kept in mind but by reading the figures downward in the table the total counts may be compared at the different intervals of preservation.

TABLE 5.—PRESERVATION OF LEUKOCYTES IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	6800*	5950	5000	3750	3300	3250	3450	2900
3	2750	2350	1400	1700	1650	2100	1850	2050
5	2750	2150	850	850	1100	1100	1600	1950
7	2550	2700	1000	550	850	1000	1400	1600
10	1700	1650	400	450	750	950	1300	1500
14	1400	1250	200	350	250	600	1400	1300
21	1000	1050	50	50	150	200	1050	800

\* Per c.mm. of blood-preservative mixture.

It will be noted that in the plain citrate mixture 21 to 25% of the leukocytes had disintegrated at the end of 3 days and from 57 to 68% within 21 days. With the M.I.H. preservative about 21.2 to 36% had disintegrated in 3 days and 74 to 100% within 21 days. With the R-T preservative 15.5 to 20% had disintegrated in 3 days and 16 to 22% within 21 days. With the M-W preservative 14.1 to 18.7% had disintegrated in 3 days and 32.8 to 35% within 21 days. Of the four preservatives employed it is observed, therefore, that the leukocytes were best preserved by the R-T and M-W preservatives carrying dextrose and dextrin respectively.

As will be shortly shown, these disintegrative changes principally affected the neutrophils and is a phase of blood preservation which has received very little attention although of probable importance in relation to the transfusion treatment of acute and chronic infections if it is granted that the administration of whole leukocytes is of benefit in treatment.



The results of differential leukocyte counts giving the percentages of neutrophils in the preserved blood are shown in Table 6. It will be noted that with the plain citrate preservative from 16.1 to 23.8% had disintegrated within 3 days; 18.8 to 20.4% in the M.I.H. preservative, 14.3 to 15% in the R-T and 18.3 to 22.4% in the M-W, while in 10 to 14 days all had disintegrated in all four preservatives in confirmation of my previous observations.<sup>8</sup> Evidently the total leukocyte counts shown in Table 5 were mostly composed of lymphocytes and monocytes as observed in these stained smears for differential counts.

TABLE 6.—PRESERVATION OF NEUTROPHILS IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	58*	57	60	53	60	66	58	55
3	36	24	32	26	40	46	26	30
5	24	24	20	26	16	12	20	24
7	8	16	12	12	12	12	12	12
10	—†	8	10	10	8	10	8	8
14	—	—	—	—	—	—	—	—
21	—	—	—	—	—	—	—	—

\* Per cent.

† Less than 8%.

Furthermore, as shown in Table 7, slight changes in the morphology and tinctorial properties of the neutrophils were observed in all specimens within the first 24 hours after collection of blood which became progressively more marked in 3 to 5 days and so advanced by 10 to 14 days as to render the cells scarcely recognizable.

TABLE 7.—MORPHOLOGIC CHANGES IN NEUTROPHILS IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	1*	1	1	1	1	1	1	1
3	2	1	2	2	1	1	1	1
5	3	3	3	3	3	3	3	3
7	4	4	3	4	4	4	3	4
10	—	4	4	4	4	4	4	4
14	—	—	—	—	—	—	—	—
21	—	—	—	—	—	—	—	—

\* 0 = morphology and staining good; 1 = slight changes; 2 = moderate changes; 3 = marked changes; 4 = severe changes; — = practically unrecognizable.

*Preservation of Platelets.* As stated in my former report<sup>8</sup> the platelets of blood preserved with plain sodium citrate showed distinct clumping immediately and 24 hours after collection with

TABLE 8.—PRESERVATION OF PLATELETS IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	265,000*	280,000	277,950	281,440	248,500	237,600	217,500	253,800
3	82,450	99,600	62,660	47,840	99,000	64,740	84,400	68,760
5	56,160	53,350	58,800	37,050	50,370	45,980	45,500	40,480
7	28,260	32,270	27,100	31,570	28,560	30,560	25,410	24,800
10	28,740	27,789	28,100	31,800	20,880	19,710	26,960	22,140
14	17,680	13,020	21,280	11,280	9,140	6,630	16,850	20,340
21	—†	—	—	—	4,520	6,730	13,720	17,300

\* Per c.mm. of preserved blood.

† Could not be counted.

evidence of deterioration in the latter. At the end of 48 hours they became scarce and after 5 days only blue chromatin masses remained. Similar changes were observed in the present study which made their counting very difficult so that the results shown in Table 8 can be regarded as only approximately correct.

It will be noted that in the plain citrate preservative the platelets were reduced by 29 to 32% within 3 days with practically none remaining at the end of 21 days. In the M.I.H. mixtures they were reduced by 44 to 49% within 3 days and likewise practically absent at the end of 21 days. In the R-T mixtures they were reduced 25 to 36.7% within 3 days but some were countable at the end of 21 days, with similar results with the M-W preservative in that 25 to 38% had disintegrated in 3 days with some still countable at the end of 21 days. The results have indicated therefore that both carbohydrate preservatives gave somewhat better preservation of platelets.

*Preservation of Prothrombin Time.* As previously stated, these determinations were made by the method of Howell as the method of Quick for prothrombin could not be employed owing to technical conditions. Rhoads and Panzer<sup>13</sup> have stated that blood preserved for a week or more is practically useless in the treatment of the acute prothrombin deficiency encountered in jaundiced patients not adequately treated with vitamin K and bile salts. In their opinion, blood in bank for 3 days would probably be of some slight value but would be so inferior to fresh blood that they recommend that only the latter be used when transfusion is intended to combat the hemorrhagic tendency in jaundice. Ziegler<sup>16</sup> also found that prothrombin decreased over a period of time in preserved citrated blood kept at 34° F. to a level of 40% of original content and states that in cases in which it is desired to raise the prothrombin content of the blood by transfusion, old banked blood is not a suitable agent. Quick<sup>12</sup> also found that the prothrombin diminishes in decalcified blood and that it is inferior to fresh blood for controlling hemorrhage in jaundice. However, the matter may be of more academic value than practical interest, since it is thought that transfusion even with fresh blood probably raises the prothrombin content of the blood of the recipient by only 6 to 8%.

As determined by the Howell method, the normal prothrombin time is about 10 minutes and, as shown in Table 9, I found the time slightly reduced with the plasmas of all preserved bloods within 24 hours after collection of blood, presumably due to an increase of thromboplastin from disintegrated platelets. This initial decrease was followed, however, by an increase of prothrombin time with the plasmas of all preserved bloods up to 7 days and apparently due to a loss of prothrombin, but curiously this was followed by a decrease of prothrombin time during the following 10 to 21 days with the plasma from the plain citrate and M.I.H. preserved bloods, while the plasmas of the carbohydrate preserved specimens (R-T

and M-W) continued to show an increased time indicative of loss of prothrombin. In this connection it is important to state that all of our determinations were of prothrombin time (Howell) and that determinations of prothrombin by the Quick method have shown deterioration in citrate preserved blood as previously stated.

TABLE 9.—PROTHROMBIN TIME OF BLOOD AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	9*	9	9	8	8	9	9	7
3	12	10	9	11	12	8	12	9
5	12	12	12	12	12	12	14	12
7	11	11	11	11	12	11	15	11
10	10	7	9	8	13	11	12	11
14	7	7	8	8	14	12	13	12
21	7	7	8	7	14	11	9	10

\* Minutes required for coagulation; method of Howell.

*Preservation of Isoagglutinins.* Not without interest is the question of the persistence of isoagglutinins for erythrocytes in preserved blood in relation to transfusion although Strumia, Wagner and Monaghan<sup>15</sup> have stated that the intravenous injection of stored plasma from citrated blood (100 cc. of 2% citrate to 500 cc. of blood) at the rate of 5.6 cc. per minute produces no reactions even though capable of agglutinating the erythrocytes of the recipient in dilutions as high as 1 to 80. Knott and Koerner,<sup>7</sup> however, state that citrated plasma may retain agglutinins for several weeks when kept at a low temperature and think it is advisable to test the erythrocytes of the recipient with a 1 to 50 dilution of stored O plasma before administration because O plasma sometimes contains agglutinins a and b in high concentration capable of quickly agglutinating the corpuscles of Groups A, B and AB.

In our study the plasmas of blood group Donor A were tested with the corpuscles of blood group Donor B and the plasmas of B with the corpuscles of A by the same microscopic method commonly employed in direct matching tests. As shown in Table 10 the plasma agglutination showed no evidences of diminution during the first 10 days with all four preservatives, while at the end of 14 and 21 days' preservation some diminution occurred which was somewhat less marked in the case of the two carbohydrate preservatives (R-T and M-W). Whether this decrease of agglutination

TABLE 10.—PRESERVATION OF ISOAGGLUTININS IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	4*	4	4	4	4	4	4	4
3	4	4	4	4	4	4	4	4
5	4	4	4	4	4	4	4	4
7	4	4	4	4	4	4	4	4
10	4	4	4	4	4	4	4	4
14	3	4	3	4	4	4	4	4
21	2	3	2	3	3	4	3	4

\* 4 = strong agglutination; 3 = moderate agglutination; 2 = weak agglutination.

was due to diminution of agglutinins in the plasmas or to insusceptibility of preserved erythrocytes to agglutination I am unable to state.

*Preservation of Complement.* As previously reported,<sup>8</sup> the complement of citrated (0.35%) human blood, kept at 4° to 6° C., was well preserved up to 14 to 21 days. Similar results have been observed in this investigation with all four preservatives as shown in Table 11, although some loss of hemolytic complement usually occurred after 7 days of preservation.

TABLE 11.—PRESERVATION OF COMPLEMENT IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	0.2*	0.2	0.3	0.3	0.3	0.3	0.3	0.3
3	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.3
5	0.2	0.2	0.3	0.3	0.3	0.5	0.3	0.3
7	0.2	0.2	0.3	0.4	0.4	0.5	0.3	0.3
10	0.2	0.2	0.4	0.4	0.5	—†	0.3	0.3
14	0.3	0.3	0.5	0.5	0.5	—	0.3	0.4
21	0.5	0.4	0.5	0.5	0.5	—	0.4	0.4

\* Amounts of plasma giving complete hemolysis.

† Incomplete hemolysis with 0.5 cc. of plasma.

These tests were conducted with the following amounts of each plasma: 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5 cc., placed in small test tubes with 0.5 cc. of 2% suspensions of washed sheep corpuscles and 1 cc. of 1 to 2000 antishoop hemolysin (2 units), followed by water-bath incubation at 37° C. for 1 hour when the readings were made. The smallest amounts of plasma giving complete hemolysis are shown in the table and, of course, these have varied according to the dilutions of blood with the various preservatives, but by reading the table downward it will be observed that remarkably good preservation of hemolytic complement was observed with all preservatives during at least the first 7 to 10 days.

*Preservation of Bactericidal Activity.* As previously reported,<sup>8</sup> the bactericidal activity of normal citrated (0.35%) human blood kept at 4° to 6° C. for *Staph. aureus*, beta-hemolytic streptococcus and *B. coli* decreased after 7 to 21 days' preservation. Similar results were observed in the present investigation employing *B. typhosus* as shown in Table 12.

All eight of the preserved bloods were cultured 24 hours, 3, 5, 7, 10 and 21 days after collection and found sterile. In conducting the tests at these intervals 3 cc. amounts of each plasma, secured

TABLE 12.—PRESERVATION OF BACTERICIDAL ACTIVITY OF BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	0*	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
7	2	0	0	0	2	3	4	4
10	3	3	3	3	3	4	4	4
21	4	4	4	4	4	4	4	4

\* 0 = no growth; 2 = slight growth; 3 = moderate growth; 4 = heavy growth.

by centrifuging, were seeded with 0.1 cc. of a 1 to 10 dilution of 18-hour broth culture of *B. typhosus* and incubated along with control cultures in broth at 37° C. for 72 hours. The controls showed good growths in 24 hours, while the results observed with the various plasmas are summarized in Table 12. It will be observed that they were completely bactericidal up to about the seventh day of preservation following which rapid deterioration in bactericidal activity occurred.

**Discussion.** It is apparent, therefore, that none of the four preservatives employed in this investigation afford adequate protection of the neutrophilic leukocytes and platelets. This phase of blood preservation has not received the attention it deserves in relation to the transfusion treatment of the acute and chronic infections as well as, possibly, in relation to the hemorrhagic states due to prothrombin deficiency. For these reasons the author has advised against the use of blood preserved for more than 3 days<sup>8</sup> for these therapeutic purposes as fresh blood appears advisable.

Possibly the same applies to the transfusion treatment of the anemias, although preserved blood appears adequate for the treatment of acute hemorrhage and surgical shock. For these purposes I believe that the addition of dextrose (modified Rous-Turner) or dextrin (Maizels and Whittaker) to the preservative is advisable, as both appear to better preserve erythrocytes than plain citrate or the preservative advocated by the Moscow Institute of Hematology as likewise found by MacDonald and Stephen,<sup>9</sup> although Boland, Craig and Jacobs<sup>3</sup> believe that the M.I.H. preservative is advisable for long preservation and plain citrate for short preservation. With these conclusions I cannot agree.

**Summary.** 1. The preservation of the blood of 2 adult donors belonging to Groups A and B by four different preservatives up to 21 days at 4° to 6° C. has been investigated. Of the four preservatives employed two were without carbohydrate (plain citrate and Moscow Institute of Hematology), one with dextrose (modified Rous-Turner) and one with dextrin (Maizels and Whittaker).

2. Examinations were made within 24 hours and at the end of 3, 5, 7, 10, 14 and 21 days' preservation for dehemoglobinization, fragility and preservation of erythrocytes, preservation of leukocytes with special reference to the neutrophils, preservation of platelets and prothrombin and the preservation of isoagglutinins, complement and bactericidal activity.

3. The two carbohydrate preservatives gave better protection of erythrocytes against dehemoglobinization, fragility and disintegration than the plain citrate and Moscow Institute of Hematology preservatives.

4. Marked reduction of the total leukocytes occurred with all four preservatives within 3 days, especially due to disintegration of the neutrophils, but the two carbohydrate preservatives gave somewhat better preservation than the two without dextrose or dextrin.

5. Marked reduction in the platelets occurred with all four preservatives within 3 days but both carbohydrate preservatives gave somewhat better preservation than the two without dextrose or dextrin.

6. A slight decrease in prothrombin time (Howell) was observed with the plasmas of all preserved bloods within the first 24 hours of collection of blood presumably due to disintegration of platelets. During the following 3 to 7 days this was followed by an increase presumably due to loss of prothrombin.

7. The isoagglutinins showed no decrease during the first 10 days with all four preservatives, but some diminution after 14 and 21 days which was somewhat less marked with the two carbohydrate preservatives.

8. Complement was well preserved by all four preservatives for the first 7 to 10 days.

9. The bactericidal activity of the plasmas for *B. typhosus* was well preserved by all four preservatives for 7 days following which rapid deterioration occurred.

**Conclusions.** Blood is better preserved by the addition of dextrose (modified Rous-Turner) or of dextrin (Maizels and Whittaker) to preservatives than by plain citrate or the Moscow Institute of Hematology methods.

Blood preserved for more than 3 days should not be used in the transfusion treatment of acute and chronic infections, the anemias and hemorrhagic states, although apparently satisfactory for the treatment of acute hemorrhage and surgical shock.\*

\* An additional advantage in the use of preserved blood may be greater safety from the danger of transfusion syphilis. I have inoculated 10 cc. of fresh citrated blood with 1 cc. of a heavy suspension of virulent *Treponema pallidum* (Nichols-Hough strain) from acute testicular syphilomas of rabbits showing approximately 200 treponemata per dark field. A rabbit inoculated at once with 1 cc. of the citrated blood-treponema mixture intratesticularly developed acute testicular syphilis in about 5 to 6 weeks, as likewise rabbits inoculated 1 to 3 hours later. Rabbits inoculated 1, 2, 7, 14 and 28 days later (the mixture being kept at 4° to 6° C.) escaped testicular infection and lymph gland transfers to fresh rabbits made 6 weeks later were negative. The results indicate, therefore, that *Treponema pallidum* in citrated blood may die after 24 hours of preservation at 4° to 6° C.

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## VITAMIN C IN CHRONIC LEAD POISONING.

## AN EXPERIMENTAL STUDY.\*

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It has been suggested that vitamins may play a rôle in heavy metal poisoning, especially with reference to the nervous system. Williams and Spies<sup>5</sup> are of the opinion that, while thiamin does not improve the condition of patients with chemical neuritis produced by tri-ortho-cresyl phosphate, there are theoretical grounds for believing that large doses of vitamin B<sub>1</sub> would act as a prophylactic.

Holmes, Campbell and Amberg<sup>4a, b</sup> treated several cases of chronic lead poisoning in factory workers and painters with large doses of vitamin C (100 to 200 mg. of ascorbic acid daily above the normal intake) and presented data to show that the vitamin treatment was more effective in removing the symptoms of lead poisoning and restoring the blood picture, than is the usual therapy with calcium or the institution of more adequate methods for reducing exposure hazards. They claim that those painters who normally have a high vitamin C intake do not develop lead poisoning; the vitamin acts as a detoxifying agent by forming poorly ionized, but soluble, lead compounds, and conversely that lead leaves less vitamin available for physiologic purposes. This is reflected in the lower urinary excretion levels of ascorbic acid as well as resemblance of the tooth and gingival changes of lead intoxication to subclinical scurvy.

These conclusions can be tested experimentally since guinea pigs respond somewhat like humans to both lead intoxication and vitamin C deficiency. Also, the technique for detecting vitamin C changes in the blood by measuring the complement titer as developed by Ecker, Pillemer, Wertheimer and Gradis<sup>3</sup> is available. Furthermore, it has been shown in this laboratory<sup>2</sup> that certain heavy metal salts may *in vitro* reversibly inactivate serum complement. It was also demonstrated that a direct correlation existed between the ascorbic acid content of serum and its complementary activity. Therefore it was of interest to discover whether chronic lead poisoning would lead to a weakening of complement. It is evident that the influence of lead poisoning on this relationship is worthy of further study.

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**Experimental.** Two experiments were conducted, one involving 46 guinea pigs and the other involving 24. The animals were placed on a diet of Purina rabbit chow which is adequate in all respects excepting vitamin C. This is present only in traces, and guinea pigs develop scurvy in 21 days on this diet. The food was not autoclaved in order to avoid destruction of other vitamins. In addition to this diet, each animal received, on alternate days, a hypodermic injection of ascorbic acid as the buffered commercial product, Cevalin, as follows:

EXPERIMENT 1.		EXPERIMENT 2.	
Mg. vitamin C.	No. animals.	Mg. vitamin C.	No. animals.
1	28	1	8
20	18	2	8
		20	8

As established in this laboratory,<sup>1</sup> 0.5 mg. of ascorbic acid daily is the minimum amount necessary for the well-being of guinea pigs *provided that environmental conditions are good*, while 10 mg. daily is the saturation level and represents the intake of the guinea pig in its normal habitat where it is accustomed to drastic environmental changes. The animals were stabilized for 1 month on this routine before lead was added to the diet.

Lead was administered as the basic carbonate,  $2\text{PbCO}_3 \cdot \text{Pb}(\text{OH})_2$ , placed in capsules and inserted in the esophagus. The following table indicates the dose of the lead compound (80% Pb) in mg. per kg. of body weight, 2 out of 3 days for 1 month.

EXPERIMENT 1.—DOSAGE OF LEAD.

Vitamin C dosage.	Median lead dosage in mg.		Range lead dosage in mg.	
	Start.	End.	Start.	End.
0.5 mg. per day . . . . .	74	95	63-88	70-108
10 mg. per day . . . . .	64	69	55-73	57-78

The doses are variable due to the fact that each animal received 40 mg. of lead compound per day, and they reflect the different weights, and at the end of the experiment the loss in weight. There is sufficient overlapping in the ranges to give a complete picture, and the variations are compensated for by the variability in absorption from the intestines. However, in the second experiment the administration was maintained at 80 mg. of basic carbonate per kg. of body weight, every 2 out of 3 days for 1 month.

**Results.** 1. *Weight Changes.* During the period of stabilization when no lead was administered, the animals on the low vitamin intake showed variation in weight; approximately one-third gained up to 10%, an equal number lost to a similar degree, and the remainder did not change. All of the animals in the high vitamin groups gained up to 15% of the original body weight. From Table 1 it will be seen that after 1 month's administration of lead, the animals receive-



ing the high vitamin level fared better than those on the lower intake. Of significance was the loss of 20% or more of body weight in 25% of the animals maintained on the minimal antiscorbutic level, whereas

TABLE 1.—WEIGHT CHANGES IN THE LEAD-TREATED GUINEA PIGS.

Treatment.	% loss.			% gain.		
	1-10.	11-20.	21-30.	1-10.	11-20.	21-30
0.5 mg. Cevalin per day plus 40 mg. lead carbonate 2 out of every 3 days for 32 days . .	11	9	6	1		
Same lead dose plus 10 mg. Cevalin per day . . . . .	12	2	1	2	1	
0.5 mg. Cevalin per day plus 80 mg. lead carbonate per kg., 2 out of every 3 days for 34 days . .	5	..	3			
Same lead dose plus 1 mg. Cevalin per day . . . . .	2	2	1	2		
Same lead dose plus 10 mg. Cevalin per day . . . . .	2	2	..	4		

in the animals on higher vitamin intakes this figure was approached only in isolated instances. The variations in weight changes encountered were not sufficiently great to rule out the effects of adding an offending agent to the diet of animals already on subminimal conditions for health.

2. *Changes in the Blood Picture.* In both experiments, the degree of plumbism attained, as measured by erythrocyte counts, hemoglobin estimation and number of stippled cells, was not materially different in the animals on different vitamin C intakes. The data are summarized in Table 2.

TABLE 2.—CHANGES IN THE BLOOD PICTURE OF GUINEA PIGS IN CHRONIC PLUMBISM.

Exp.	Animal.	Stabilization period.			After 1 month of lead.		
		R.B.C.*	% Hb.†	Stipple cells.‡	R.B.C.	% Hb.	Stipple cells.
		<i>0.5 Mg. Cevalin Daily.</i>					
1 . .	A 5451	5.85	90	0	4.25	60	4
1 . .	A 5425	5.20	80	0	2.90	60	6
1 . .	A 5032	5.15	90	0	2.75	50	35
1 . .	A 5465	4.95	90	0	3.95	60	22
2 . .	A 5387	4.20	75	0	3.85	60	36
<i>1 Mg. Cevalin Daily.</i>							
2 . .	B 5389	5.00	75	0	3.55	60	48
2 . .	B 5384	5.35	70	0	2.90	50	20
<i>10 Mg. Cevalin Daily.</i>							
1 . .	B 5453	5.10	90	0	3.70	65	21
1 . .	B 4853	5.20	85	0	3.95	90	31
1 . .	B 5404	5.05	90	0	3.30	55	14
1 . .	B 5464	5.05	80	0	3.95	60	9
1 . .	B 5459	5.80	100	0	3.65	60	26
1 . .	B 5472	5.45	80	0	3.45	70	15
2 . .	C 5380	5.35	70	0	2.30	50	52
2 . .	C 5379	4.90	75	0	3.15	50	58

\* Millions of red blood cells.

† Tallqvist estimation.

‡ Number per 20 high-power fields.

3. *Changes in Complement Function and Serum Ascorbic Acid Levels.* Ecker, Pillemmer, Wertheimer and Gradis<sup>3</sup> showed that a parallelism exists between the ascorbic acid concentration of the guinea pig serum and its complementary activity, and that the parallelism holds true until a definite level of ascorbic acid is attained at about 1 mg. per 100 cc. of serum. At this point the complementary activity reaches its maximal efficiency. In the course of this study it was also noted that this parallelism occurs even in the presence of chronic lead poisoning. The results are given in Chart 1. It will be seen that the degree of complementary activity

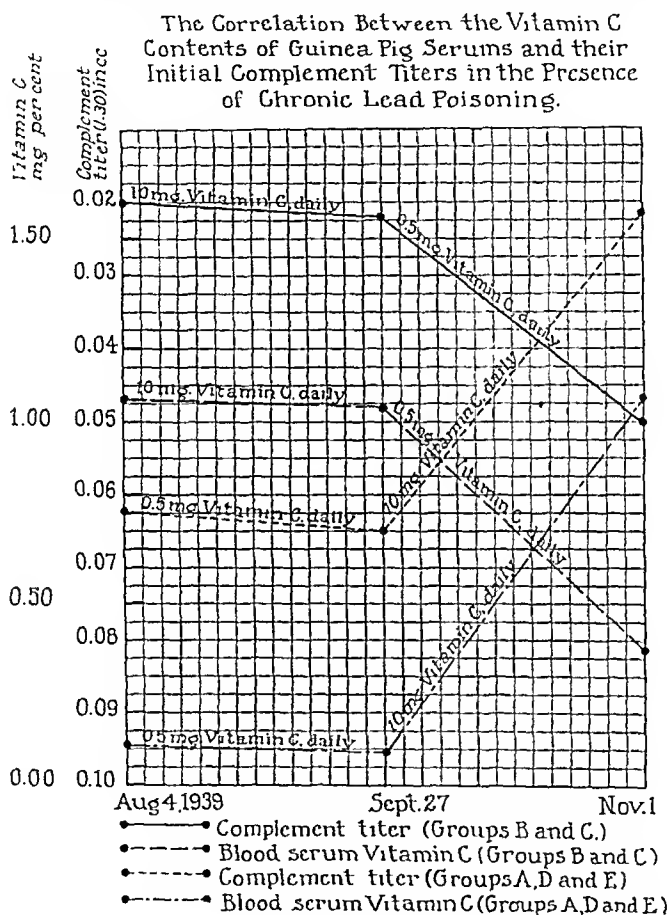


CHART 1

is dependent on the content of ascorbic acid in the serum. Holmes and his co-workers stated that the possible action of ascorbic acid in alleviating lead poisoning was the formation of a poorly ionized, but soluble, lead ascorbate complex. If this were true, it would be expected that a reduction of complementary activity as well as the blood serum ascorbic acid content would follow. However, this is not the case. The observations confirm the earlier work from this laboratory and indicate that the formation of a lead ascorbate complex does not occur.

4. *Deposition of Lead in the Organs.* The determinations of lead in the organs were made by the Kettering Laboratory of Applied Science, University of Cincinnati, Cincinnati, Ohio, and are here listed:

Tissue.	No. 5379. 10 mg. vit. C/day.		No. 5392. 10 mg. vit. C/day.		No. 5381. 0.5 mg. vit. C/day.		No. 5383. 0.5 mg. vit. C/day.	
	Mg. Pb per 100 gm.	Ratio kidney = 100.	Mg. Pb per 100 gm.	Ratio kidney = 100.	Mg. Pb per 100 gm.	Ratio kidney = 100.	Mg. Pb per 100 gm.	Ratio kidney = 100.
Kidney . .	15.0	100.0	20.0	100.0	5.0	100	23.0	100.0
Liver . .	7.0	46.5	4.6	23.0	1.6	32	1.55	6.74
Bone . .	7.8	52.0	16.0	80.0	10.0	200	14.4	62.6
Brain . .	0.58	3.87	0.17	0.85	0.2	4	0.25	1.1

The analytic data expressed as mg. of Pb per 100 gm. fresh tissue do not show any clear-cut effect of vitamin C on lead storage. They do suggest that the deposition of lead in the liver tends to be greater when the animal is on a saturation diet of vitamin C. The data were not sufficiently extensive to be conclusive. If the results are expressed as ratios (kidney = 100), the above mentioned effect is not so decisive. It is also worthy of note that, regardless of vitamin intake, the deposition of lead in the kidney was several times that of the liver. In acute and chronic lead poisoning in man the reverse is true.

5. *Paralysis, Convulsions and Death.* Here, the beneficial effects of a high ascorbic acid intake were striking and appear to be unequivocal. In both experiments, only 2 of the 26 guinea pigs on the high vitamin C régime developed clear-cut spasticities or paralyzes, and none of the pigs died of lead poisoning during the period of observation. On the other hand, 18 of the 44 animals on the low ascorbic acid intake developed some form of neuro-plumbism and 12 died of typical lead poisoning. Of the 18 animals which developed neuro-plumbism, 4 showed signs of spasticity and clumsiness, 5 spasticity and paralysis, and 9 developed convulsions.

6. *Vitamin C as a Therapeutic Agent in Lead Poisoning.* When 15 of the animals originally on 0.5 mg. Cevalin daily had received lead for 1 month, and were in frank plumbism, they were taken off the lead diet, and 7 of these were retained on the low vitamin level and 8 were raised to the daily 10 mg. Cevalin level. Both groups showed a rapid weight gain, increase in erythrocyte count, and disappearance of stippled cells. The degree of recovery in 1 month was not strikingly greater in the high vitamin group as compared to the lower vitamin group. In contrast to its prophylactic action, ascorbic acid failed to show any beneficial effect on the spasticities and paralyzes. The results are shown below:

#### WEIGHT CHANGES IN POISONED GUINEA PIGS TAKEN OFF LEAD.

Continued on 0.5 mg. Cevalin daily.

% stabilized weight restored.	No. animals.
90-100 . . . . .	3
100-110 . . . . .	2
127 . . . . .	1

Raised to 10 mg. Cevalin daily.

% stabilized weight restored.	No. animals.
74 . . . . .	1
90-100 . . . . .	2
100-110 . . . . .	4
117 . . . . .	1

## BLOOD PICTURE UNDER SIMILAR CONDITIONS.

% increased R.B.C.	% increased Hb.	Stippled cells.	% increased R.B.C.	% increased Hb.	Stippled cells.
10	25	0	40	16	0
24	20	0	60	50	0

**Summary and Conclusions.** 1. In two series of 44 guinea pigs on a subclinical scurvy intake of vitamin C, the degree of lead poisoning developed in 1 month by oral ingestion of basic lead carbonate was more severe when compared to the plumbism in two groups of 24 pigs on a saturation level of the vitamin.

2. The vitamin was not significantly protective against weight loss, anemia and stippling.

3. The vitamin was effective in preventing the onset of neuroplumbism.

4. No evidence has been found to show that lead has any effect on vitamin C utilization or its metabolism.

5. As a therapeutic procedure, vitamin C is inefficient as compared to removal of exposure to lead.

6. Complementary activity of the serum of the animals in lead poisoning was parallel to the ascorbic acid concentration of the serum, and was not influenced by the lead intake.

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## THE PLASMA COAGULATION TIME AS A SIMPLE TEST FOR VITAMIN K DEFICIENCY.\*

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VITAMIN K deficiency in chicks causes a hemorrhagic diathesis characterized by a diminution in the amount of thermolabile blood globulins (prothrombin) associated with prolonged blood and plasma coagulation times, and traumatic and spontaneous hemorrhages. It is now evident that a similar hemorrhagic tendency may

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develop in humans in certain cases of hepatitis, obstructive jaundice,<sup>9</sup> the hemorrhagic diathesis of the new born,<sup>10</sup> and in a few other disorders<sup>1b,2,13</sup> due to vitamin K deficiency. Consequently, a simple clinical test for a deficiency of this vitamin is highly desirable. Quick's test of prothrombin time<sup>5</sup> and that of Ziffen and his co-worker at Iowa<sup>12</sup> were devised for this purpose, but they present certain technical difficulties which limit their use. Howell's test of prothrombin time has met with a number of objections, chief of which are that it does not measure prothrombin and that it varies with the concentration of platelets present in the blood plasma, the time and speed of centrifugation, the temperature, the quantity of calcium added, and certain other variables.

As this report is concerned with the technique and serviceability of a simple clinical test to determine the desirability of administering vitamin K therapeutically, the theories of blood coagulation<sup>3</sup> and their relationship to the recently discovered vitamin<sup>8</sup> need not be reviewed again. The proposed test of blood plasma coagulation time is a modification of Howell's test of prothrombin time. It is based on the fact that the recalcified plasma of oxalated normal blood will usually coagulate in a given length of time and that in hemophilia and in pronounced cases of vitamin K deficiency the time is considerably longer than normal. The many factors which influence the test but slightly become relatively unimportant in the procedure as outlined, as the test has shown a consistent uniformity under normal conditions and a definite departure from normal in certain hemorrhagic diatheses.

It has been carried out 125 times on the blood of 100 normal individuals and 110 times on 59 patients with disorders unrelated to hemorrhagic conditions and deficiency states; and 64 times on normal chickens. It has also been carried out 105 times on 40 cases of biliary tract disease, some of which have already been reported,<sup>1b,6</sup> on patients with hemophilia and purpura, and on 85 chicks in various stages of vitamin K deficiency.

**Technique.** Whole blood is obtained by a clean venepuncture and added to a previously oxalated centrifuge tube. The standard amount of oxalate used is 10 mg. per 5 cc. of blood, using the dry potassium salt. A number of tubes containing sufficient oxalate for 2, 5, or 10 cc. of blood may be prepared in advance. The oxalated blood is then centrifuged for 5 minutes at 3500 revolutions per minute in a constant speed Gyro centrifuge.<sup>7</sup> The clear plasma is then pipetted off. Four small chemically clean test tubes,  $\frac{3}{8}$  inch in diameter, are then set up with varying amounts of 0.4% calcium chloride solution. The first tube contains 0.5 cc. (2 mg. calcium chloride); the second 0.4 cc. (1.6 mg. calcium chloride); the third 0.2 cc. (0.8 mg. calcium chloride); and the fourth 0.1 cc. (0.4 mg. calcium chloride). Two-tenths centimeters of the plasma to be tested is added to each of the tubes and they are shaken briskly about 10 times without corking or inverting. The time that a firm clot forms in each tube (will not flow when tube is held horizontally) is noted, and the length of time recorded from the mixing

of the plasma and calcium chloride to the time of clot formation is the plasma coagulation time for each of the 4 calcium chloride dilutions. The shortest time recorded is the coagulation time of the plasma, while the longest time recorded is the plasma coagulation time with an excess of calcium which is 2 to 5 times the optimum amount.

The use of 10 mg. of dry potassium oxalate per 5 cc. of blood was selected because this amount of oxalate is in general use already.<sup>11</sup> A high speed centrifuge was chosen with a time limit of 5 minutes because such a centrifuge has already been utilized for blood studies by Rytand<sup>7</sup> and does away with irregularities in speed and time. Centrifuging the blood more slowly over a longer period of time will apparently give comparable results.

In the Quick technique for determining prothrombin times, solutions of oxalate and calcium chloride are used which permit an excess of calcium to be added which makes the results inconsistent and usually produces a prolonged time because of an excess of calcium.<sup>4</sup> In developing the technique of the present test, a standard amount of oxalate per cm. of blood was selected and varying amounts of calcium added to the plasma in order to determine the exact range where optimum calcification occurred to produce the shortest clotting time.

In conducting these studies 3 sets of 10 tubes each were set up, each series containing diminishing amounts of 0.4% calcium chloride as follows: 1.0 cc., 0.9 cc., 0.8 cc., 0.7 cc., 0.6 cc., 0.5 cc., 0.4 cc., 0.3 cc., 0.2 cc., and 0.1 cc. To each tube was added 0.2 cc. of plasma; blood from 3 different patients being used for each series. It was noted that clotting was most rapid in the second half of the tubes and that the differences from tube to tube in the second half tended to be very slight. In setting up a similar series of 6 tubes containing the following amount of calcium, 2 mg., 1.6 mg., 1.2 mg., 0.8 mg., 0.4 mg., and 0.2 mg., the most rapid clot formation nearly always occurred in the fourth (0.8 mg.), or the fifth (0.4 mg.) tube. Out of 45 such studies, the most rapid clotting occurred 17 times in the 0.4 tube, 17 in the 0.8; in 10 it was the same in both tubes, and it occurred once in the 1.2 mg. tube. These optimum times never occurred in the 2 mg., the 1.6 mg., or the 0.2 mg. tubes. Coagulation occurred in the last tube only once and did not occur in the 0.4 mg. tube on 8 occasions. The longest time usually occurred in the first tube but the times for the first and second tube were often identical or very nearly the same. Consequently, in setting up routine tests, the 2 mg., 1.6 mg., 0.8 mg., and 0.4 mg. tubes only were retained. In 100 tests using 4 tubes, the most rapid clotting occurred in the third tube in 38%, in the fourth tube in 29%, and was the same in the third and fourth tubes in 33%. No clotting at all took place in the fourth tube in 11% of the tests. The first and second tubes are of no additional value in normal tests; but when the plasma coagulation time tends to be prolonged, the tendency is often much more pronounced when an excessive amount of calcium is present than in the tubes containing an optimum amount of calcium.<sup>1b</sup> A number of tubes containing the four solutions of 0.4% calcium chloride (0.5 cc., 0.4 cc., 0.2 cc., and 0.1 cc.) may be made up at a time, stoppered, and put away for future use. Dry calcium chloride tends to cause irregular results apparently because of improper mixing with the plasma.

All tests have been run at room temperature which has varied between 68 and 80° F. The higher temperatures tend to produce slightly more rapid coagulation, but serial tests on the same patient on 5 different days with a variation in laboratory temperature of 12° F. did not alter the coagulation time more than 1 minute above or below the average reading.

Preferably the test should be carried out within 30 minutes after the blood has been drawn, as the rapidity of plasma coagulation tends to diminish after standing 1 or more hours at room temperature. However, in testing the stability of plasma coagulation in 41 normal patients 2 hours after the

blood was drawn, it was found that the time was not increased over the initial reading in 13 (31.7%) and was still within normal limits in 18 (43.9%) more. In 7 of the remaining 10 it was only 9, 1 minute above the normal limit. In the other 3 it was 10, 12, and 13 minutes respectively. When it was retested in 23 patients after 4 hours, it was not increased in 6; was still within normal limits in 7 more; and ranged between 9 and 20 minutes in the 10 remaining plasmas. When the plasma coagulation time is longer than normal, the tendency to prolongation on standing at room temperature is more pronounced. It is also more pronounced in the tubes containing an excess of calcium.

The accuracy of the test is well shown by studying the plasma coagulation time on separate specimens of blood taken at hourly intervals. This was done coincident with a standard glucose tolerance test on 3 individuals. The results are shown in Table 1. The variation in the times was only 1 to 2 minutes when an optimum amount of calcium was used and only 2 to 3 when an excess was used.

TABLE 1.—PLASMA COAGULATION TIMES ON SPECIMENS OF BLOOD TAKEN HOURLY DURING A GLUCOSE TOLERANCE TEST. ONLY SLIGHT VARIATIONS OCCUR. COAGULATION TIME IN MINUTES.

Case.	Amount of Ca.	1st hr.	2d hr.	3d hr.	4th hr.	5th hr.	Variation.
F. A. . . .	Optimum	5	6	6	7	..	2
	Excess	7	9	10	9	..	3
J. B. . . .	Optimum	6	6	6	7	6	1
	Excess	7	7	7	9	7	2
M. F. . . .	Optimum	7	9	7	8	..	2
	Excess	11	12	13	12	..	2

Only 0.8 cc. of blood plasma is required for the test. This amount is readily obtained from 2.5 cc. of whole blood. If less blood is available, the test can be carried out with 0.4 cc. of plasma by adding 0.1 cc. of plasma to each of the 4 tubes which contain only one-half the usual amount of 0.4% calcium chloride (0.25 cc., 0.2 cc., 0.1 cc., and 0.05 cc.). Occasionally homogeneous, firm clots do not form, but a small pellicle becomes solid or a partial web-like clot occurs. In such instances which are most likely to take place when the coagulation time is prolonged, the end point should be read at the time a firm clot forms whether or not the whole solution is involved. The exact cause of such partial clotting is not known.

Ordinarily the whole technical procedure from the time of drawing the blood to setting up the 4 tubes to read the coagulation time takes on the average about 8 minutes. The method has the advantage of requiring only 2 stable solutions (2.0% potassium oxalate and 0.4% calcium chloride). No unstable tissue extracts need be added, and no constant temperature water bath is required.

**Results of Plasma Coagulation Time Tests in 100 Normal Subjects.** The test was carried out on 13 normal medical students, 18 normal student nurses, and on 69 patients without evidence of organic disease. (See Table 2 and Chart 1.) Their ages varied between 16 and 60. There were 38 males and 62 females. The average normal plasma coagulation time was found to be 5.38 minutes, varying between 2 and 8 minutes when an optimum of calcium is added. When an excessive amount of calcium is added, the average normal time was found to be 8.61 minutes with the limits of variation lying between 3 and 15

minutes. The blood coagulation times for the same group of normal individuals is also shown in Table 2. The average time is 5.27 minutes, with the limits of variation lying between 3 and 11.

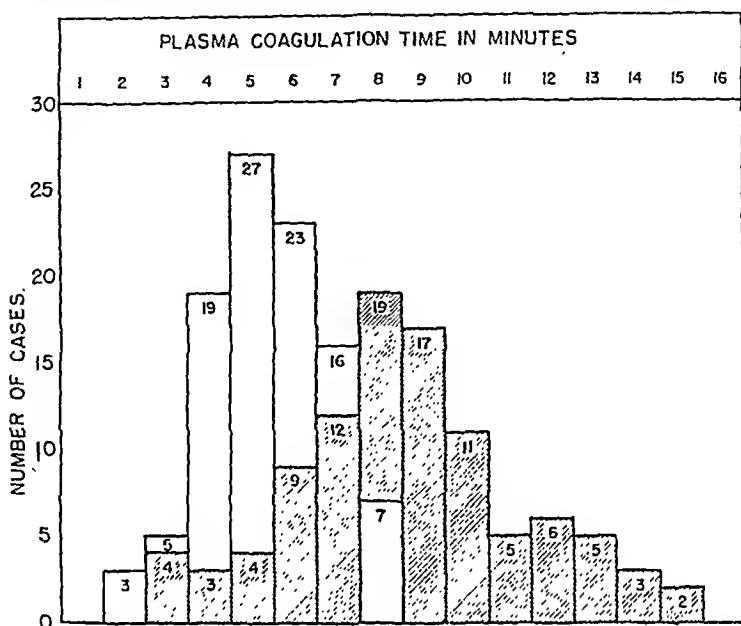


CHART 1.—Distribution of normal plasma coagulation times in 100 individuals. White blocks = coagulation time with optimum amount of calcium; cross-hatched blocks = coagulation time with excess of calcium.

**Results of Plasma Coagulation Time Tests in 149 Chicks.** Vitamin K deficient chicks were raised in the laboratory as previously described.<sup>1b</sup> The study of normal chicks was of necessity confined to birds on a similar diet receiving adequate amounts of vitamin K, usually as a supplement of alfalfa to the diet. Blood studies were

TABLE 2.—BLOOD AND PLASMA COAGULATION TIMES; DISTRIBUTION OF 100 NORMAL CASES BY INCIDENCE PER NUMBER OF MINUTES.

Number	Coagulation time in minutes.															Av.
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Blood	0	0	8	33	30	9	8	5	1	4	2	0	0	0	0	5.27
Plasma with optimum Ca.	0	3	5	19	27	23	16	7	0	0	0	0	0	0	0	5.38
Plasma with excess Ca.	0	0	4	3	4	9	12	19	17	10	5	6	5	3	2	8.61

carried out on chicks which were usually 3 and 4 weeks of age but occasionally older chicks were used. Normal blood coagulation time was taken as 1 to 10 minutes, as previously noted<sup>1,8</sup> but with variation up to 30 minutes in a few rare instances. No opportunity has been offered to study the plasma coagulation time of chicks on the range. Consequently, those chicks with an adequate diet and



a normal blood coagulation time have been considered normal as far as their plasma coagulation was concerned. Table 3 presents the results of these studies in 64 normal chicks, and Table 4 shows the results of similar tests in 85 fowls with vitamin K deficiency.

TABLE 3.—THE BLOOD AND PLASMA COAGULATION TIMES IN 64 NORMAL CHICKS ON A DIET ADEQUATE IN VITAMIN K. COAGULATION TIMES IN MINUTES.

Blood.	Plasma.	Blood.	Plasma.	Blood.	Plasma.	Blood.	Plasma.
$\frac{1}{2}$	(c)*	2	(c)*	2	9	4	3
$\frac{1}{2}$	5	2	2	2	9	4	4
1	(c)*	2	3	2	10	4	7
1	(c)*	2	3	2	10	4	9
1	1	2	5	2	12	4	9
1	1	2	5	2	13	4	10
1	2	2	5	2	13	5	1
1	2	2	5	2 $\frac{1}{2}$	8	5	1
1	2	2	5	3	(c)*	5	5
1	6	2	5	3	2	5	6
1 $\frac{1}{2}$	2	2	5	3	7	5	8
2	(c)*	2	6	3	7	5	9
2	(c)*	2	6	3	8	5	11
2	(c)*	2	6	4	(c)*	5	15
2	(c)*	2	6	4	(c)	6	4
2	(c)*	2	8	4	1*	6	10

\* Blood coagulated in oxalated tube.

The birds have been divided into four groups according to the length of time it took their blood and plasma to coagulate. Group 1 includes 20 birds in which the deficiency seemed doubtful or borderline. These birds were on a deficient diet but their blood coagulation times were within normal limits although greater than the normal average. None of the plasma coagulation times was over 30 minutes in the group. Group 2 is composed of 30 birds with a moderate deficiency. The blood coagulation times were longer than the average in all but 2 instances, but all were still within the normal limit of variation. However, all the plasma coagulation times were moderately to greatly prolonged. Group 3 consists of 17 birds with marked vitamin K deficiency showing prolonged blood and plasma coagulation times. Group 4 is composed of 8 birds with a total deficiency. The blood and plasma showed no tendency to coagulation in 10 to 48 hours of observation. The last three groups with the prolonged times showed the usual tendency to both spontaneous and traumatic hemorrhages, the tendency increasing with each group. The times found in Groups 1 and 2 and more rarely in 3 correspond to similar studies in vitamin K deficient patients.

Serial studies of the blood and plasma coagulation times were carried out in a number of birds receiving vitamin K therapy. Four deficient birds were tested and placed on a dietary supplement of 25% alfalfa and the coagulation times followed over a period of 30 days. All the birds showed similar results. The findings in 2 are charted in Chart 2 and show the reduction in blood and plasma coagulation times to normal. In a similar group of 3 birds a single

TABLE 4.—BLOOD AND PLASMA COAGULATION TIMES IN 85 CHICKS WITH VARYING DEGREES OF VITAMIN K DEFICIENCY.\*

Doubtful deficiency.		Moderate deficiency.		Marked deficiency.		Total deficiency.	
Blood.	Plasma.	Blood.	Plasma.	Blood.	Plasma.	Blood.	Plasma.
7 min.	2 min.	1½ min.	35 min.	30 min.	> 7 hrs.	> 10 hrs.	> 10 hrs.
7 "	7 "	4 "	56 "	33 "	> 48 "	> 24 "	> 24 "
7 "	9 "	5 "	1 hr. 27 min.	34 "	> 24 "	> 24 "	> 24 "
7 "	13 "	8 "	43 min.	40 "	1 hr. 29 min.	> 24 "	> 24 "
7 "	22 "	8 "	> 12 hrs.	42 "	43 min.	> 24 "	> 24 "
8 "	11 "	9 "	1 hr. 32 min.	42 "	> 48 hrs.	> 48 "	> 48 "
8 "	24 "	10 "	31 min.	60 "	> 12 "	> 48 "	> 48 "
9 "	16 "	11 "	40 "	60 "	> 24 "	> 48 "	> 48 "
10 "	24 "	11 "	1 hr. 31 min.	1 hr. 1 min.	> 48 "		
12 "	25 "	11 "	> 24 hrs.	1 hr. 2 min.	24 "		
12½ "	20 "	12 "	31 min.	1 hr. 3 min.	> 24 "		
12½ "	21 "	12 "	36 "	1 hr. 12 min.	1 hr. 22 min.		
13 "	14 "	12 "	36 "	1 hr. 13 min.	2 hrs. 12 min.		
13 "	20 "	12 "	54 "	1 hr. 18 min.	2 hrs.		
14 "	16 "	12½ "	36 "	1 hr. 25 min.	2 hrs. 28 min.		
17 "	23 "	13 "	> 60 hrs.	7 hrs.	> 48 hrs.		
19 "	23 "	15 "	> 12 "	48 "	> 48 "		
20 "	9 "	15 "	> 24 "				
20 "	22 "	16 "	> 4 "				
23 "	11 "	17 "	5 hrs. 53 min.				
		18 "	1 hr. 13 min.				
		18 "	> 3 hrs.				
		18 "	> 4 "				
		19 "	53 "				
		21 "	> 48 "				
		24 "	> 48 "				
		26 "	> 48 "				
		27 "	31 min.				
		27 "	2 hrs. 29 min.				
		29 "	> 24 hrs.				

\* Many birds in the last two groups bled to death.

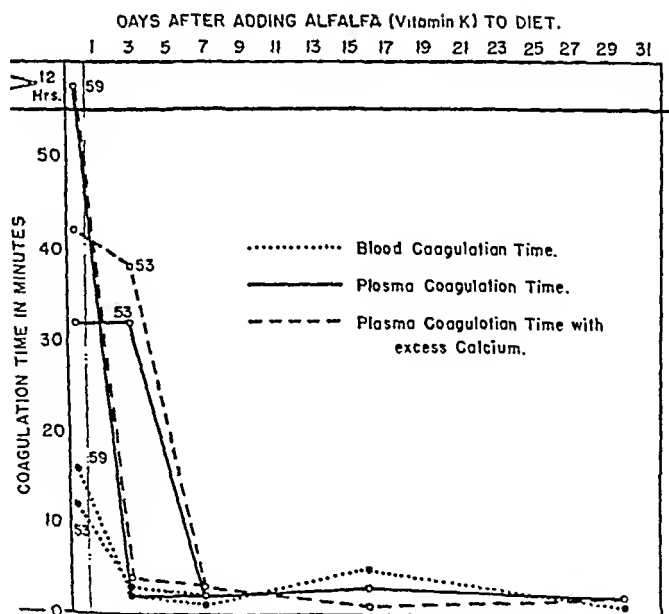


CHART 2.—Reduction in blood and plasma coagulation times to normal on adding alfalfa to the diet of 2 vitamin K deficient chicks (No. 53 and No. 59).

dose of 1 mg. of vitamin K orally reduced the times to normal overnight. Subsequently the birds were kept on a vitamin K deficient diet only. Gradual prolongation of the coagulation times occurred

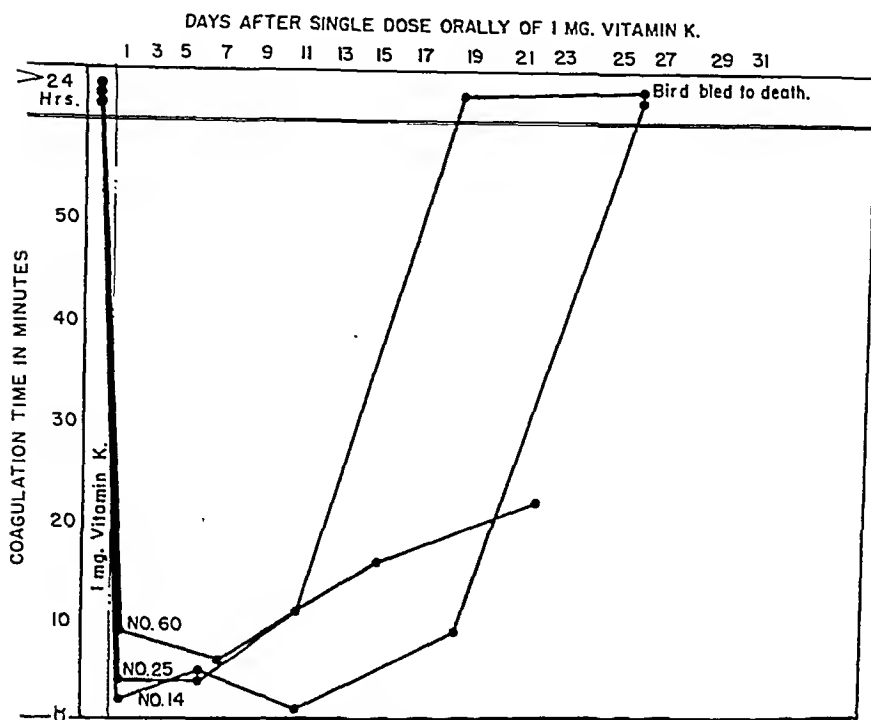


CHART 3.—Effect of a single dose of vitamin K on the plasma coagulation times of 3 chicks fed on a vitamin K deficient diet. Rapid fall to normal with gradual prolongation after the first 11 days. Failure of coagulation in 2 birds on the 26th day with fatal hemorrhage in 1.

in all three birds, resulting in death from hemorrhage in one as shown in Chart 3. A group of 6 birds was similarly treated with a single dose of 2 mg. of synthetic vitamin K (2-methyl-1-4 naphthoquinone).

TABLE 5.—REDUCTION OF BOTH BLOOD AND PLASMA COAGULATION TIMES TO NORMAL IN 3 VITAMIN K DEFICIENT CHICKS 24 HOURS AFTER A SINGLE INTRAMUSCULAR INJECTION OF 2 MG. SYNTHETIC VITAMIN K. PERSISTENCE OF NORMAL TIMES FOR 9 DAYS SHOWN IN 2 BIRDS.

Bird No.			Coagulation time before injection of vitamin K.	Coagulation time after injection of vitamin K.	
				24 hrs.	9 days.
39	Plasma	Blood	15 min.	1 min.	2 min.
		Optimum Ca.	>24 hrs.	1 "	2 "
		Excess Ca.	>24 "	2 "	3 "
62	Plasma	Blood	11 min.	1 min.	1 min.
		Optimum Ca.	1 hr. 31 min.	2 "	2 "
		Excess Ca.	1 " 38 "	3 "	3 "
69	Plasma	Blood	12 min.	1/2 min.	
		Optimum Ca.	25 "	1/2 "	
		Excess Ca.	1 hr. 3 min.	2 "	

They all responded rapidly within 40 to 60 minutes. The blood changes in 1 are recorded graphically in Chart 4A. Synthetic vit-

amin K in 2 mg. doses (4-amino-2-methyl-naphthol hydrochloride)\* was injected intramuscularly into 3 birds with vitamin K deficiency. As shown in Table 5 all showed a reduction to normal coagulation times by the next day, and 2 were still normal nine days later, despite the continuation of the deficient diet. Similar intramuscular injections in 1 mg. doses were given to 12 birds. The blood and plasma coagulation times were very rapidly reduced, usually within 20 to 30 minutes, reaching normal well within an hour. A typical example is given in Chart 4B.

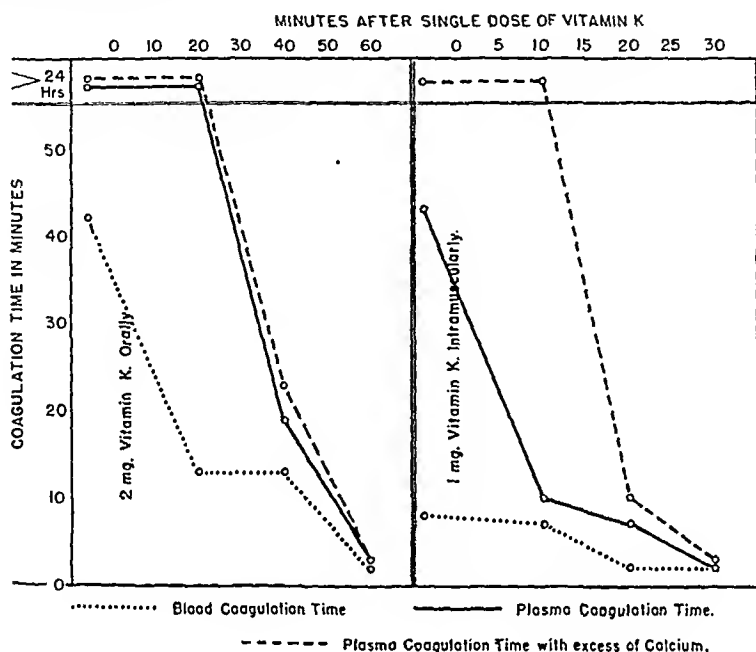


CHART 4.—Effect of single large dose of synthetic vitamin K on the blood and plasma coagulation times in vitamin K deficient chicks. Normal within 60 minutes after administration by mouth in A and within 30 minutes after injection in B.

The results of the plasma coagulation time studies in these chicks, particularly when serial tests were carried out relative to vitamin K administration, show the test to be highly satisfactory in following experimentally controlled vitamin K deficiency and tend to substantiate the results of the tests obtained in normal and vitamin K deficient humans.

**Vitamin K Deficiency in Man.** The plasma coagulation time has been studied in 40 cases of liver and biliary tract disease in man. The test has proven just as satisfactory as in the studies with chicks. Three case studies have already been reported showing pronounced deficiency and return to normal findings coincident with the administration of vitamin K preparations.<sup>1b,6</sup> The effect of vitamin K therapy in patients with obstructive jaundice is well illustrated

\* Supplied by Parke-Davis & Co.

in Chart 5. The relationship of the plasma coagulation time to treatment is shown in a patient with a slight deficiency, a patient with a moderate deficiency, and a patient with a marked deficiency complicated by hemorrhage. The improvement in plasma coagulation is consistent in each instance and the charts are very similar to those shown for chicks.

The plasma coagulation time was studied in 10 patients with thrombocytopenic purpura. All were found to be within normal limits despite the presence of active bleeding in several.

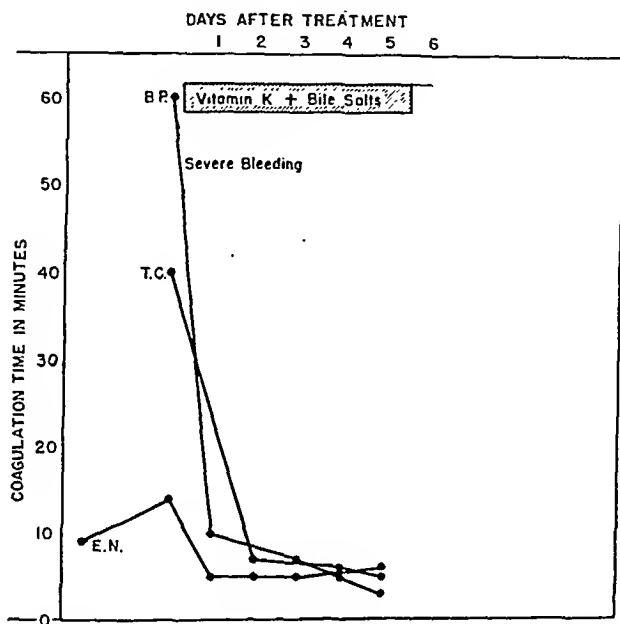


CHART 5.—Reduction of plasma coagulation times in 3 patients with obstructive jaundice coincident with vitamin K and bile salt therapy. The cases represent different degrees of deficiency. All became normal by the second day.

**Summary.** 1. A technique for measuring the plasma coagulation time of recalcified oxalated blood plasma has been outlined which is a modification of Howell's measurement of prothrombin time.

2. The technique of the test is simple to carry out and gives results which are sufficiently constant to be reliable for clinical use. No unstable tissue extracts are required.

3. Normal standards of plasma coagulation time have been obtained based on a study of the blood of 100 normal individuals.

4. The suitability of the plasma coagulation time as a test for vitamin K deficiency has been shown in a study of the blood of 149 chicks, 85 of which were vitamin K deficient.

5. The test has proven satisfactory in the diagnosis and treatment of jaundiced patients with vitamin K deficiency.

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## A QRS PATTERN OF DIAGNOSTIC VALUE IN THE ELECTROCARDIOGRAM

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THERE is a continually increasing number of reports on electrocardiographic changes described as diagnostic or characteristic of the various types of heart disease. To be of value in the interpretation of clinical records, such changes must occur in tracings from diseased hearts and at the same time be absent, or extremely rare, in those obtained from normal hearts. Likewise, the greater the frequency of changes in electrocardiographic records from diseased hearts, particularly in the absence of accepted electrocardiographic evidence of heart disease, the more important they become in diagnosis. The changes in the QRS complex about to be described, we believe, answer these requirements and justify a report.

The characteristics of the curves under consideration may be seen by inspection of the examples given in Chart 1. It can be noted that the QRS complex in Lead I is directed chiefly upward, while in Lead III it is directed chiefly downward. These changes are characteristic of left axis deviation. However, inspection of the QRS group in Lead II shows that, unlike the usual curve of left axis deviation,  $R_2$  is greater than  $R_1$ .  $S_3$  is decidedly out of phase with  $R_2$ , occurring later. The first portion of the QRS group, if plotted on Einthoven's triangle, shows directional components in the range of so-called normal axis deviation ( $+90$  to  $+30$  degrees),

whereas the latter portion of the *QRS* group shows an unusual rotation of the directional component counterclockwise into the range usually called left axis deviation.

To determine the possible significance of such curves, search was made in the files of the Heart Station of The Charity Hospital for all electrocardiograms which displayed a major upward deflection in Lead I, a major downward deflection in Lead III, and  $R_2$  greater than  $R_1$ . Curves were selected only when the *QRS* time intervals were in normal range (less than 0.1 sec.) and when  $S_3$  was 6 mm., or greater, with proper standardization. The reasons for discarding curves with the amplitude of  $S_3$  less than this arbitrary level will become evident below. In 19,000 curves, 61 (0.32%) satisfied the criteria laid down. In every instance the axis index was within normal range. This is in the range of frequency of such conditions

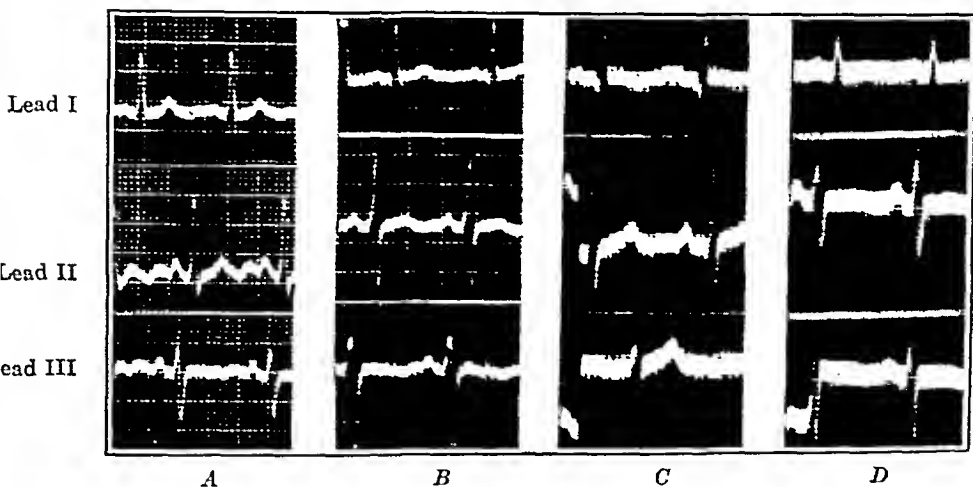


CHART 1.—Examples of the *QRS* pattern described in the text. A, B, and C with "high"  $R_1$ , D with "low"  $R_1$ .

as ventricular paroxysmal tachycardia and complete auriculo-ventricular heart block. In 57, there were sufficient data to establish the presence or absence of heart disease. Of these, 54 (94.7%) were known definitely to have heart disease.

These tracings were then classified in three ways: 1, according to the height of  $R_1$ ; 2, according to the presence or absence of other electrocardiographic evidences of heart disease (such as inverted  $T_1$ ); and 3, according to diagnosis, to elicit the possible causes of the changes. In the first group division was made into curves with  $R_1$  greater than 5 mm., and those with  $R_1$  5 mm. or less (Chart 1). It was found that in the group with low  $R_1$  the percentage of diseased hearts was 83.3. With the taller  $R_1$ , all but one (97.7%) showed definite heart disease. The second grouping, according to the presence or absence of other electrocardiographic evidences of

heart disease, indicated that a significant percentage (59%) of such *QRS* changes occurred when no other electrocardiographic evidence of myocardial disease was present. Of these, 90.6% had definite evidence of heart disease, and when the patients showing high complexes in Lead I and normal *T* waves are considered, 95% had definite heart disease. The third grouping, according to diagnosis, showed that almost invariably curves of this type occurred in patients with types of heart disease that produced strain upon the left ventricle. In the group with tall  $R_1$ , 36 of the 45 patients with adequate data for diagnosis had either arteriosclerotic or hypertensive heart disease, or both. Six had syphilitic heart disease, 1 rheumatic heart disease, 1 beriberi, and 1 severe anemia. With low  $R_1$ , there were 4 patients with arteriosclerotic and hypertensive heart disease, 3 with syphilitic heart disease, 2 with rheumatic heart disease, 1 with toxic myocarditis and definite *T* wave changes, and 2 with no heart disease.

**Discussion.** As stated above, casual inspection of the tracings in Chart 1 leads to discovery of changes which set them apart from ordinary left axis deviation.  $R_2$  is greater than  $R_1$  and  $S_3$  occurs late in relationship to these two waves. The first portions of the curves corresponding to  $R_1$  and  $R_2$  show an axis between  $+30$  and  $+90$  degrees which rotates markedly near the end of the *QRS* complex to a negative value. This rotation of the electrical axis sets these curves apart both from normal and from usual left axis deviation. The problem arises as to when this rotation becomes abnormal. In practical terms, it involves the determination of when, under these circumstances, the magnitude of  $S_3$  becomes abnormal. If one covers most of the  $S_3$  of Chart 1A, then the remainder of the curve in view in all three leads appears normal. If then one exposes more and more of  $S_3$ , when will one state that the curve is abnormal? Such a criterion would depend, as stated in the introduction to this paper, upon the height and frequency of  $S_3$  when  $R_2$  exceeds  $R_1$  in the electrocardiograms of normal individuals.

Search of the literature on these points reveals little information of value. Values for  $S_3$  reported in the literature by Lewis,<sup>3</sup> Wilson,<sup>5</sup> Chamberlain and Hay,<sup>1</sup> and Jensen, Smith and Cartwright<sup>2</sup> for normal individuals from the first to the seventh decade of life, vary from 0 to 13 mm. Included in all these groups, however, are tracings of the usual type of left axis deviation with  $R_2$  smaller than  $R_1$ . We have been unable to find in the literature any values for curves of the type we are reporting. In Wilson's report on 104 normal individuals, elimination of the tracing with an  $S_3$  of 13 mm., known to be a curve with typical left axis deviation, reduced the maximum value for  $S_3$  to 4.5 mm. Lewis in 52 healthy subjects found a maximum  $S_3$  of 4 mm.; axis deviation was not stated. In the 19,000 tracings from which the present group was taken, only 3 (0.015%), with an  $S_3$  of 6 mm. or more were known to be normal. From 0 to



5 mm. there were many tracings from normal individuals, all of which were discarded. From these data, 6 mm. appears to be the borderline of normal limits, although we cannot say that an occasional or rare normal individual will not exceed it. However, such examples have not been found by us in the literature.

The establishment of such criteria, although the borderline may be indecisive, permits further interpretation of our tracings with abnormal *T* waves. Since such *T* wave changes stamp the curve as abnormal in any case, the establishment of such *QRS* changes in the absence of other electrocardiographic evidence of heart disease is important in their evaluation as a sign of heart disease. The absence of these changes in normal hearts is also necessary. Since the data support such findings, one can assume that the *QRS* changes are further evidence to support the *T* wave abnormalities. The frequent occurrence together of inverted  $T_1$  and the *QRS* changes would be expected from the correlation of the latter with the diagnosis.  $T_1$  inversion, as a sign of myocardial disease, is characteristic of left ventricular lesions, and the diagnosis in the presence of the *QRS* changes herein reported, whether in association with  $T_1$  inversion or not, is almost invariably one affecting the left ventricle.

Deep  $S_2$  and  $S_3$  in left ventricular disease, as well as  $T_1$  inversion, are changes known to result from anterior myocardial infarction. In such instances,  $R_1$  often becomes diminished in size. Two instances of myocardial infarction are included in the present group. Inspection of many curves of anterior myocardial infarction from the literature indicates that the *QRS* relationships here stressed sometimes occur in this condition.

Whereas the curves of anterior myocardial infarction falling into the present group have been accompanied by *T* wave changes, there is another similar group with normal *T* waves which deserves mention. These are patients of asthenic habitus, without organic heart disease, who display, instead of a tendency toward right axis deviation with low  $R_1$ , a left axis deviation with low  $R_1$ . Two such patients have been reported by one of us.<sup>4</sup> In these,  $R_2$  equalled  $R_1$  in one and exceeded it in the other. We have studied the curves of some others, while eliminating tracings which fell short of the criteria for the present study. Although such findings, unlike the tendency to right axis deviation, are not common with the ptotic heart, they do occur, apparently as the result of unusual rotation or peculiarities of Purkinje architecture, and indicate that the only consistent electrocardiographic finding in ptotic heart is a low  $R_1$ . Two of the patients in the presently reported group appear to fall in this category, with  $R_2$  greater than  $R_1$ , and account for our division of the cases into a "low"  $R_1$  and "high"  $R_1$  group. Elimination of such patients is necessary before the criteria given can be used in the "low"  $R_1$  group as diagnostic of myocardial changes.

**Conclusion.** A *QRS* pattern is described which has been found to occur in tracings from patients with heart disease in the absence of any other electrocardiographic evidence of heart disease. It promises to be of value in electrocardiographic interpretation.

We wish to thank Dr. Richard Ashman, Director of the Heart Station, Charity Hospital of Louisiana, for the privilege of using the records analyzed.

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### THE VASCULAR "SPIDER" ASSOCIATED WITH CIRRHOSIS OF THE LIVER.

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THE vascular "spider" (nævus araneus; spider telangiectasis; spider angioma) is a bright red lesion, characterized by a central point from which radiate fine, hairlike branches for a distance of about 1 cm. Because of this configuration it also has been called stellate nævus (étoile vasculaire). The central point, or core, is generally of pinhead size and is barely palpable. However, larger centers, from one to several millimeters in diameter, may be distinctly elevated. Vascular spiders are seen usually on the skin of the face, arms, fingers, and upper trunk, and only occasionally on the lower trunk and legs. At times they appear to favor sites of previous injury to the skin, as from furuncles or puncture wounds. They also occur in mucous membranes of the nasal septum, lips, tongue, conjunctivæ, and less often of the gastro-intestinal or genito-urinary tracts. Lesions in the mucous membranes are prone to bleed. Our interest in the spider was aroused by its high incidence in liver disease and by the occurrence of three spurting hemorrhages arising from these tiny spots—one on the lip, one on the arm, and one on the thorax—none of which was of a size large enough to suggest the rare pulsating angioma described in the literature.

The occurrence of a congenital form (hereditary multiple telangiectases or angiomas; Rendu-Osler disease) was established by the studies of Rendu<sup>24</sup> and of Osler.<sup>22</sup> Their observations have received confirmation in many subsequent case reports.<sup>10,25</sup>

In 1890 Hanot<sup>15</sup> observed their frequent association with liver disease. Osler,<sup>22</sup> Bouchard,<sup>4</sup> Gilbert and Herscher,<sup>8</sup> and others have also noted this coincidence. However, no data are available on the actual incidence of these lesions in persons with liver disease. Of 63 patients with cirrhosis of the liver, studied by us, 48 exhibited these structures. It is not unusual to see fresh lesions appear while others disappear in the course of the disease. Fiessinger<sup>6</sup> expressed the opinion that they were of prognostic significance, since they disappeared in certain patients who made clinical recovery. Bloomfield<sup>2</sup> described one such instance.

There are uncertainties as to the nature of the vascular spider. It is not clear from the literature on this subject whether the structure is on the arterial or venous side of the vascular tree, or whether it represents a dilatation or a new growth of vessels. These lesions have been described simply as vascular channels,<sup>1,9,14</sup> as venous dilatations,<sup>3,22</sup> and as arterial naevi or angiomas.<sup>8,17,19</sup> In other reports, a larger pulsating form has been described as a rare and peculiar type of lesion.<sup>28-30</sup>

It is noteworthy that Gilbert and Herscher in 1903 observed pulsations in these lesions, and on this account they considered them to be arterial angiomas. Steinmann<sup>26</sup> observed that they faded when pressure was applied to the central point. Fiessinger<sup>6</sup> concurred in these findings. The present report confirms the latter observations. In addition to studies on the direction of flow within the vessels and on pulsations, these structures have been examined with regard to intravascular pressure, contractility, reaction to drugs, and histologic characteristics.

**Observations.** *Direction of Flow.* When a point of pressure is applied to the central core of the spider, the smaller branching blood-vessels empty. Pressure applied at the periphery does not influence the central point. The flow, therefore, is directed from the center towards the periphery.

*Pulsation.* It is possible, even on palpation of the very small spiders, to feel a definite, though feeble, pulsation. The application of a cover glass over a spider with sufficient pressure produces regularly a rhythmic flush and pallor that synchronizes with the subject's radial pulse.

In order to quantitate the pulsation, a procedure was devised by which a magnified image of the vessel excursion could be observed. A mirror, about 1 mm. square, was fixed to the spider by collodion or egg white. A control mirror was fixed to an adjacent area of the skin, about 1 cm. distant. In a dark room, a beam of light was directed at the mirrors, which reflected magnified images on the

ceiling. In the case of spiders on the wrist or fingers a frank pulsation arose from the mirrors adfixed to the vessels, but none from the controls. However, when mirrors were located on the trunk or near a large artery, the controls likewise pulsated, due (it seemed) to vibrations transmitted from nearby arteries.

*Pressure Within the Spider.* One patient exhibited several typical spiders on the forearm, which were selected for study. On elevating the arm above the head, the superficial arm veins emptied, whereas the spiders remained full of blood. With the subject's arm held upright, a sphygmomanometer cuff was applied to the upper arm above the spider, and the pressure was raised to 170 mm. Hg. The spider was then stroked with the finger until it blanched. After the arm was lowered to a plane level with the heart, pressure was released within the cuff. The spider filled abruptly when the pressure was reduced to 85 mm. Hg. This study was confirmed by use of the reflecting mirrors previously described. When the pressure in the cuff was raised above 85 mm. Hg the pulsations ceased. They reappeared when the pressure was lowered to 85 mm. Hg or less. Systolic blood pressure at the brachial artery was 120 mm. Hg. It appears, therefore, that the pressure at which blood flows through the vessels of the spider is lower than the systolic pressure of the brachial artery and higher than the subject's venous pressure. Moreover, it is higher than the pressures ordinarily observed in the skin capillaries.<sup>18</sup>

*Dilatation and Contraction.* A fair definition of the structure of the spider was obtained by use of the dissecting microscope with a 40 $\times$  magnification of Figure 1. Interfering glare of light from the skin was eliminated by applying a drop of oil to the under surface of a cover glass placed on top of the spider. Dilatation and contraction of the central vessel wall was visible in spiders of moderate size. The pulsation was augmented by exerting counterpressure on the cover glass. With this technique, pulsation was revealed even in the smaller vessels. However, in the small radiating branches, the pulsation was seen to be associated with a to-and-fro rush of blood through the long axis of the vessels. These branches were many times larger than capillaries at the finger nailbeds seen with the same magnification.

In the course of these studies with the dissecting microscope it became apparent that vascular changes in the skin of patients with liver disease were not confined to the spider. In 8 out of 15 patients with cirrhosis of the liver and vascular spiders, the skin of the arms revealed diffuse vascularity in other areas beyond the immediate vicinity of the spider. The vascularity was characterized by a network of widely dilated blood-vessels. In none of 15 control hospital patients were these changes observed. When erythema of normal skin was produced by rubbing with gauze, many fine capillaries with numerous punctate hemorrhages were seen, but no vessel

dilatation comparable to those described. Therefore, it is possible that the spider may indicate the presence of a widespread vascular change. This has been suggested by Fiessinger.<sup>6</sup>

*Pharmacologic Reactions.* An attempt was made to observe the reactivity of the spider vessels to local stimuli. The intracutaneous injection of 0.1 cc. of 1:1000 solution of adrenalin hydrochloride at 1 cm. distance caused an area of blanching with a peripheral zone of hyperemia. As the pale area encroached upon the spider it caused marked narrowing of the finer vessels and moderate constriction of the larger central vessel. The intracutaneous injection of 0.05 cc. histaminic phosphate (1:1000 solution) at a like distance was followed by a spreading pink flare. As this enveloped the spider, many tiny vessels (? capillaries) appeared. The larger vessels also seemed widened. However, due to limitations of technique it was not possible to measure these changes in a quantitative fashion.

*Histologic Structure.* Seven vascular spiders have been examined histologically; 2 specimens were obtained by biopsy and 5 at autopsy. In 4 instances the lesions were located on the dorsum of the forearm and in 3 instances on the anterior aspect of the thorax. Since these structures fade after death, it was necessary to outline areas for the purpose of identification before death.

The blocks of skin varied in their greatest dimension from 0.5 to 2.5 cm. The tissue was fixed in Zenker's solution for 18 hours, washed in tap water for 24 hours, dehydrated in alcohol, cleared in cedarwood oil, and embedded in paraffin. Serial sections, 6 $\mu$  in thickness, were cut parallel to the skin surface. They were stained with Weigert's elastic tissue stain and hematoxylin, and they were counterstained with eosin.

On microscopic examination the vascular spider was seen to arise from an artery in the subcutis. This was observed in all instances. Histologically there are two distinct types. In one type the central vessel of the spider branches into smaller arteries which have the usual arterial structure. The smaller arteries branch successively into arterioles and capillaries. This was observed in 2 of 7 cases. The other type of vascular spider (seen in 5 cases) is quite different, and for the sake of convenience is described as the "glomus" type.

This latter type has a characteristic morphology. The afferent artery is of medium size, with a single layer of endothelium resting on an internal elastic lamella, and a media composed of circular muscle fibers. At the junction of this artery with the central vessel of the spider the endothelium and the internal elastic lamella become separated by a thick layer of cells with elongated, oval nuclei, abundant cytoplasm, and indistinct cell borders. The nuclei are about as long and half again as wide as those of the smooth muscle cells of the arterial media. They have a more diffuse distribution of chromatin and they are more widely separated. From

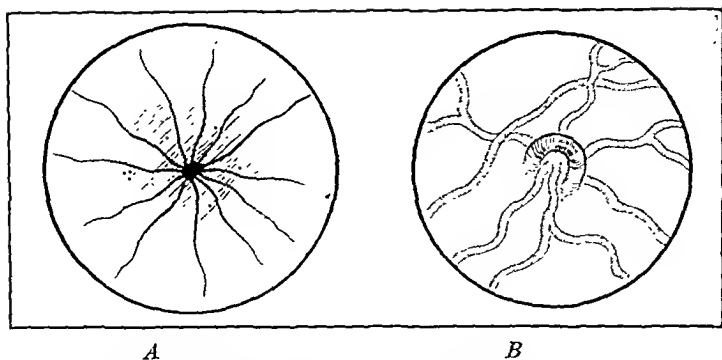


FIG. 1.—*A*, Typical vascular spider as seen with naked eye. *B*, Typical vascular spider as seen with dissecting microscope ( $\times 40$ ).



FIG. 2.—Section of part of the glomic connection between the afferent artery and the vascular "spider." The superior portion of the field is proximal to the afferent artery and shows the outer circular fibers of the media with elastica separating the newly acquired inner media. The inferior, more distal portion, has a much thicker inner layer of cells with elongated nuclei oriented in various directions. Here the stretched elastic lamella is still present but shows fragmentation in the lower part of the field. (Van Gieson elastic tissue and hematoxylin-eosin stain.  $\times 230$ .)



FIG. 3.—A major branch of the vessel seen in Figure 2. Note the absence of both an outer circular layer and elastic fibrils. The wall consists of cells like those of the inner media of the latter. (Van Gieson elastic tissue and hematoxylin and cosin.  $\times 110$ .)



FIG. 4.—Small branches of the vessel seen in Figure 3. The walls consist of cells several layers thick, smaller and more closely spaced than those of Figure 3. These vessels branch into capillaries. (Van Gieson elastic tissue and hematoxylin-cosin stains.  $\times 110$ .)

the varying shapes and directions of the long axes of the nuclei the cells seem to run circularly, longitudinally, and diagonally. The internal elastic lamella and the media of circular muscle of the afferent artery continue into the central vessel to form the outer portion of its wall. In the central vessel the elastic lamella becomes thinner, loses its wavy character and finally disappears after breaking into delicate threads (Fig. 2). The muscle fibers of the outer media retain the circular direction present in the afferent artery.

In its salient features, this junction of the afferent artery with the central vessel of the spider has the histologic traits of the "glomus," so thoroughly described by Popoff<sup>23</sup> and others.<sup>5,13,16,20,27</sup> However, it differs from the typical glomus by forming branches which ultimately connect with capillaries, instead of forming arteriovenous shunts or anastomoses. The central vessel follows a tortuous path through the corium, and near the dermis it branches into several smaller vessels. These branches retain the single layer of endothelium and the inner cellular layer, but they lack the outer coat of circular muscle. In these branches the media are 3 to 4 cells thick. The nuclei appear denser, smaller, and more darkly stained than those of the central vessel (cf. Fig. 3). These branches divide into smaller vessels of the same type and ultimately connect with capillaries, as seen in Figure 4.

Neither of the types of "vascular spider" resembles a tumor. The simpler type, consisting of dilated arteries, probably results from hyperplasia or hypertrophy of preëxisting arteries. It is unlikely that a physiologic or functional change alone could make arteries of this size visible through the skin. The more complex type with vessels resembling the afferent arteries of the glomus, suggests a metaplastic change of an artery to resemble glomus vessels and hyperplasia of the newly formed vessels. There are several reasons for this interpretation. *First*, these latter structures were found in regions where the glomus (arteriovenous anastomoses) has not been described. *Second*, the glomus vessels of the spider branch into capillaries and do not connect directly with veins. This implies that they are not derived from preëxisting arteriovenous anastomoses. *Third*, these vascular spiders tend to increase in size and number during exacerbations of the signs of cirrhosis, whereas they regress or even disappear during remissions of the disease.

**Discussion.** Congenital telangiectases have been described as dilated vascular channels lined by a single layer of endothelium, but lacking coats of elastic tissue and smooth muscle.<sup>6,9,14</sup> Osler and Bogaert believed them to be venous dilatations. Memmesheimer<sup>21</sup> pointed out associated degenerative changes in the supporting tissues. His cases, however, resembled diffuse venous ectasia rather than vascular spiders.

In several descriptions of telangiectases associated with liver disease an arterial structure has been implied. Gilbert and Herscher<sup>8</sup>



described a conglomeration of vessels of varying size, with irregular lumen, with swollen endothelium, and with a vessel wall usually thickened and studded with many nuclei. Loeper<sup>19</sup> and his associates interpreted the vessels as new formed arterioles. Weber<sup>28</sup> described one case of "pulsating stellate nævus" consisting of a superficial layer of dilated capillaries and beneath these, in the deeper cutis, a spiral or plexiform artery.

In the present studies certain of these differences possibly may be reconciled if the level of the histologic sections, as related to the skin surface, is taken into consideration. The superficial branches of the vessels, indeed, are vascular channels, whose walls are composed of a single layer of endothelium. On following the course of these branches in serial sections, they are seen to emanate from a larger vessel; tortuous, thick-walled, and finally conforming in its structure to an artery.

The preceding observations reveal that the vascular spider originates from the arterial side of the vascular tree and that it is of the order of a small artery. This is demonstrated by studies on the direction of blood flow, pulsations, contractility, intravascular pressure, and histologic structure of the vascular spider. The response to the injection of adrenalin and of histamine likewise is consistent with the behavior of an artery or of an arteriovenous anastomosis.<sup>11,12</sup>

The problem has been complicated by the interchangeable use of the terms "spider telangiectasis" and "spider angioma" for these structures. The term telangiectasis is restricted usually to small lesions, as described in this report, whereas angioma refers to the larger, elevated lesions. Since both actually do pulsate, and since both are seen frequently in the same patient, it is likely that the differences are more in degree than kind.

It is assumed in the literature that the congenital and the acquired lesions are similar. The acquired type of spider, described in this paper, does not conform to descriptions of the congenital lesions, previously mentioned. Also it is clear from the present studies that the vascular spider should not be confused with *congenital hemangioma*.

There have been several reports suggesting a causal relationship between the vascular spider seen in liver disease and the congenital spider.<sup>7,28-30</sup> These are based on case reports in which vascular lesions appeared in advance of clinical signs of liver disease. The inference has been drawn that this process may share a background in common with liver disease. It should be pointed out that cirrhosis of the liver may long antedate any clinical evidence of the disease. Indeed, it may remain clinically latent throughout life. Consequently, in those cases lacking a family history of vascular spiders, latent disease of the liver may exist.

**Conclusions.** 1. The vascular spider, associated with disease of the liver, has the physiologic characteristics of an artery. This has

been demonstrated by studies on direction of blood flow, pulsations, contractility, intravascular pressure, and pharmacologic reactions.

2. In serial sections, the histologic characteristics of 2 lesions are those of an artery and its arteriolar branches. In 5 others they resemble, in a magnified form, the arterial segment of an arteriovenous anastomosis (glomus). However, the branches of these vessels are continued into capillaries, and are not directed into veins.

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## TEMPERATURE AND BRAIN METABOLISM\*

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CHANGES of body temperature have been widely used as therapeutic agents. Increased temperature has been successfully employed in the treatment of general paresis and in gonorrheal infec-

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tion. The present report is concerned with the effects of temperature changes on cerebral metabolism.

**Method.** Metabolism of the brain *in vivo* was estimated from chemical analyses of the arterial and venous blood entering and leaving the brain. Samples of blood coming from the brain were taken from the internal jugular vein by the method of Myerson, Halloran and Hirsch<sup>5</sup> and the arterial blood samples were collected without contamination with air and analyzed for oxygen and carbon dioxide content,<sup>7</sup> glucose,<sup>3</sup> and lactic acid.<sup>2</sup> The oxygen capacity of the arterial blood was determined in each case. The velocity of blood flow in the peripheral circulation was estimated by the cyanide circulation time method of Robb and Weiss.<sup>6</sup>

The effect of fever therapy on the cerebral metabolism was studied on 15 patients suffering with general paresis. Observations were made before the rise of temperature and at various intervals during the period temperature was elevated. In 7 instances fever was induced by the injection of 0.4 cc. of triple typhoid vaccine intravenously. In 7 others temperature was raised with inductotherm and 1 patient was studied during malarial fever. These studies were not limited to patients. The metabolism of excised cerebral tissues was estimated at various temperatures from 25° C. to 45° C. Cerebral cortex of rats were minced and the oxygen uptake was determined in the Warburg apparatus.

**Results.** It should be emphasized that with all three methods of producing fever, the effects in general were the same, that is, the metabolic A:V oxygen differences increased. In a typical example, Patient 11 (Table 1), the oxygen difference at a temperature of 98° F. is 5.15 vol. % and at 104.4° F. rises to 7.61 vol. %. Finally, at 106° F., a value of 9.14 vol. % is attained. In 11 of 15 patients the oxygen difference increased at least 2 vol. % during fever. The results of the oxygen capacity of the blood revealed no significant changes in 8 instances but 3 increases and 5 decreases were also observed. The oxygen capacity varies with the number of red blood cells and is therefore an indicator of the concentration of the blood. Because of the profuse perspiration during the fever, an increased concentration of the blood might be expected but the liberal ingestion of fluids probably overcame such a change.

The A:V difference of glucose disclosed an absorption of glucose by the brain in 45 of 49 experiments. In only one case did the brain pour a significant amount of glucose into the blood. No relationship between the volume of oxygen and the amount of glucose absorbed by the brain was observed. The concentration of lactic acid frequently was moderately increased by fever but in most cases the lactic acid content of blood was not changed significantly as a result of passage through the brain.

The observations on the effect of temperature on the metabolism of excised brain tissue are presented in Table 2 and Chart I. It may be seen in Chart I that the metabolic rate of the brain increases from 25° C. to 44° C. during a period of observation of 20 minutes. The rate of increase from 25° C. to 30° C. is 7.3%; from 30° C. to 35° C., 9.2%; from 35° C. to 40° C., 8.4%; and from 40° C. to

TABLE 1.—OBSERVATIONS MADE DURING THREE TYPES OF FEVER THERAPY.  
INDUCTOTHERM THERAPY.

INDUCTOTHERM THERAPY.						Arterial.	
Patient No.	Temp., °C.	Oxygen, A:V diff.	Circulation time.	Blood pressure.	Pulse.	Lactic acid.	Sugar.
Inductotherm Therapy.							
1 . .	99.4	5.16	17.0	150/72	100	17	81
	101.8	5.05	10.0	156/106	90	20	90
	103.8	7.24	7.0	104/96	120	31	141
2 . .	100.8	6.91	15.4	156/110	100	16	97
	103.8	10.99	11.8	147/75	160	25	101
3 . .	98.6	9.37	14.0	122/90	88	13	110
	102.6	7.46	9.2	176/130	130	31	127
	104.0	11.38	7.2	160/100	130	24	124
4 . .	98.6	6.36	16.0	90/50	90	12	83
	101.8	5.85	15.0	104/58	90	13	77
	102.6	6.66	12.2	104/50	120	24	88
	105.0	10.62	10.0	112/38	122	21	88
5 . .	99.4	5.30	18.0	92/60	90	22	81
	101.4	3.68	12.2	100/60	70	12	94
	103.0	2.61	9.2	112/60	86	17	101
	104.8	5.39	10.4	106/50	96	21	105
6 . .	99.0	4.62	11.0	117/68	90	16	77
	101.0	6.60	13.0	122/80	100	16	79
	103.6	7.29	9.0	136/60	120	16	88
	105.4	7.86	7.4	134/70	120	19	98
7 . .	98.6	6.62	13.2	134/90	88	26	97
	103.4	7.70	11.0	134/90	140	22	97
	105.6	8.05	9.6	118/80	140	26	110
	106.0	6.31	7.2	134/90	120	24	110
Typhoid Therapy.							
8 . .	98.6	7.75	20.0	126/94	80	15	95
	105.0	15.82	17.0	138/86	120	36	119
9 . .	98.8	6.93	15.0	126/90	80	26	92
	105.0	7.88	11.0	108/50	100	46	112
	105.3	7.09	4.0	100/50	130	31	129
10 . .	98.8	4.91	13.0	104/70	88	17	79
	101.6	6.98	10.6	94/42	110	16	95
	104.0	7.17	9.0	100/60	130	28	90
11 . .	98.0	5.15	17.6	158/106	78	20	97
	100.4	6.55	11.0	156/96	108	20	92
	102.0	6.63	10.0	155/70	96	27	84
	104.4	7.61	13.0	140/62	130	17	102
	106.0	9.14	7.4	125/70	140	27	129
12 . .	98.6	10.26	22.0	122/80	80	22	99
	101.2	10.83	13.0	120/70	100	20	100
	105.6	9.32	14.0	120/60	120	27	119
13 . .	98.6	4.45	12.4	120/70	80	11	72
	100.8	8.21	15.6	90/30	120	20	74
	103.0	8.76	21.8	96/35	132	26	77
14 . .	98.8	5.15	14.4	117/80	90	15	131
	102.8	8.66	14.8	90/80	100	19	93
	105.4	10.17	13.6	84/62	130	21	92
	103.8	10.60	18.8	98/68	100	25	110
Malarial Therapy.							
15 . .	99.0	3.56	17.0	116/70	84	..	122
	102.0	6.18	14.2	104/70	100	..	159
	104.2	9.34	12.6	110/50	100	..	141

44° C., 6.2%. However, above 44° C. or 111° F., this increase is not maintained. This is seen more clearly in the lower curve which presents the observations made during the 50th and 60th minutes and reveals a rapid fall of the oxygen uptake with temperatures above 40° C.

TABLE 2.—TEMPERATURE AND CEREBRAL METABOLISM.

Oxygen uptake is calculated per 100 mg. of minced rat brain per hour.

Temperature.	0 to 20 minutes.		50 to 60 minutes.	
	Number of observations.	Average oxygen uptake.	Number of observations.	Average oxygen uptake.
25° C.	14	69	11	51
30° C.	11	100	10	85
33° C.	9	131	9	105
37° C.	37	189	34	182
38° C.	19	216	19	183
40° C.	24	245	19	176
42° C.	45	263	21	139
44° C.	27	315	23	80
45° C.	19	310	18	44

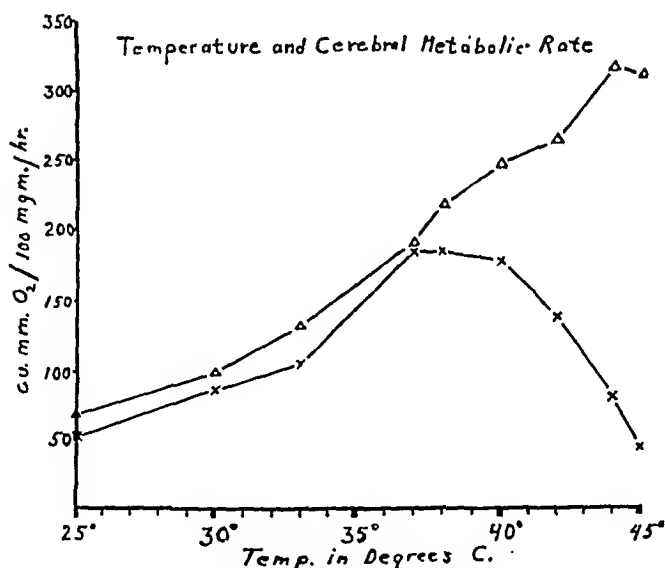


CHART I.—Upper curve indicates metabolic rate for first 20 minutes at various temperatures. Lower curve indicates metabolic rate from 50th to 60th minutes.

**Discussion.** The present results reveal that the brain takes part in the increased oxygen uptake of the body which is characteristic of fever. DuBois<sup>1</sup> has observed an average rise of 13% in the metabolic rate of the body for each degree Centigrade. An apparent augmentation of cerebral metabolism is indicated by an increase of the A:V difference greater than expected from DuBois' observations. For example, in Experiment 11, a rise of 8° F. should elevate metabolism approximately 55%, yet the change of the A:V difference from

5.15 vol. % to 9.14 vol. % represents an acceleration of 77%. Such an increase may be explained in one of two ways: 1, the brain responds with a rise in metabolism greater than other parts of the body during fever; or 2, the circulation rate through the brain is slower during fever thus making for a larger A:V difference.

Other evidence indicates that the blood flow through the brain may be diminished during fever, or at least not increased to the same extent as the cerebral oxygen uptake. It is well known that elevation of body temperature is combated principally by greater loss of heat from the body. Heat losses are mediated by an increased blood flow through the periphery. This redistribution of the circulating volume deprives the other parts of the body, including the brain, of the quota of blood. An increased blood flow through the periphery is indicated by: 1, the shorter circulation time observed with the cyanide method of Robb and Weiss; and, 2, a vasodilation evidenced by the warm flushed skin of the patients. It, therefore, seems probable that cerebral circulation is often diminished by fever and that the increase of metabolism is not as great as indicated by the A:V differences.

In order to obtain further information on this point and exclude the factor of blood flow, the metabolism of excised cerebral tissues was studied at various temperatures from 25° C. to 45° C. An acceleration of metabolism was noted in all temperatures from 25° C. to 44° C. for the first 20 minutes. Up to a temperature of 44° C. metabolism is accelerated for the first 20 minutes as seen in the upper curve, but the lower curve which shows the effect on metabolism from the 50th to the 60th minutes reveals a depression at temperatures above 40° C. It is apparent that some changes detrimental to cerebral oxidation occur at high temperatures. These alterations may be the cause for the occasional death which is observed with hyperpyrexia.<sup>4</sup>

Three chief principles are active in normal metabolism: oxygen, enzymes, and food. During fever the interactions of these three principles are accelerated. Oxygen is utilized more rapidly and the temperature of the body is raised, but this process cannot be accelerated indefinitely. With regard to temperature, enzymes are formed of two parts, first, thermostabile, and, second, thermolabile, protein in nature. With increasing temperature a point will be reached at which the protein parts of the enzyme systems are changed. Until this critical temperature of the protein parts of the enzyme is reached, the delivery of energy for cerebral metabolism is accelerated, but after the proteins are changed, the enzyme can no longer take part in the delivery of cerebral energy. Thus, as the cell proteins are changed by the heat, the cells must simultaneously die for want of the energy necessary to keep them alive. This is well illustrated by the results obtained on excised minced cerebral tissues. As the temperatures rise above 37° C. the rate of acceleration is not main-

tained even for the first 20 minutes. During the 50th to the 60th minutes this decrease is more pronounced and especially so with temperature from 40° C. to 44° C. Dixon studied rates of respiration in sliced cortex of the rabbit's brain and stated that respiration was only slightly higher at 42° C. than at 37° C. At 45° C., however, respiration was increased 100% above that at 37° C. In the present observations the increment between 37° C. and 42° C. was 39% and the one between 37° C. and 44° C. was 66% for the first 20 minutes. The increase of respiration from 30° C. to 37° C. is 90%. Thus the increase from 30° C. to 37° C., is in good agreement with DuBois' observations while the rise from 37° C. to 44° C. is smaller. This smaller increment with the higher temperature may be attributed to the greater susceptibility of excised cerebral tissue to increase of temperature. Such a factor may be emphasized because rat brain possesses a high rate of metabolism and may therefore suffer more from a rise of temperature. On the other hand, DuBois' observations may not apply directly to the brain for they were made on the entire respiratory exchanges of patients and not on the brain alone.

Finally a word may be said in regard to the effect of fever on the course of general paresis. As suggested above, increase of temperature may damage brain and the therapeutic effect may be ascribed in part to the greater susceptibility of the diseased portions which may thus be destroyed. Another factor may be more important and this depends upon the development of a non-specific defense against the *spirocheta pallida*. This is general tissue response as evidenced by the increased protein content and greater cell count of cerebral spinal fluid of the luetic patient. It is well known that patients with such a reaction have a better prognosis and moreover derive benefit from fever therapy. These defensive responses are probably based on enzymatic activities. The latter are accelerated by fever and account at least in part, for the benefit derived from this form of therapy.

**Conclusions.** Fifteen patients with general paresis were subjected to one of three forms of fever therapy and the arterial A:V differences of the cerebral blood were determined. In 11 of 15 instances the A:V difference increased by more than 2 vol. %. In most cases the augmentation of the A:V difference was greater than could be explained by the rise of temperature. Such a large increase may be due to changes in blood flow not commensurate with those of the oxygen uptake of the brain. In minced cerebral tissues from rats the increase of respiration from 30° C. to 37° C. is 90%, in accordance with expectation of chemical reactions. In contrast the rise from 37° C. to 44° C. is only 66%. This damaging effect of high temperature is increased with duration.

Though the results of changes of temperature are many, they are mediated chiefly by the effects of enzyme systems which make energy available for the body. With rise of temperature these

systems yield a more rapid flow of energy thus accelerating all actions. However, an increase of temperature which is critical may cause an irreversible change of the thermolabile portion of these enzymes, thus interfering with delivery of energy and in extreme cases causing death.

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## PATHOLOGIC CHANGES FOLLOWING PROLONGED ADMINISTRATION OF SULFATHIAZOLE AND SULFAPYRIDINE.

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FOLLOWING the synthesis of 2(p-amino-benzene-sulfonamido)thiazole by Fosbinder and Walter<sup>7</sup> and Lott and Bergeim,<sup>15</sup> studies have been made of its pharmacology, toxicology and therapeutic activity.<sup>2,4,9,10,12,16,18,24,25</sup> The lesions produced in laboratory animals by prolonged administration of sulfathiazole and sulfapyridine have also been studied.

Shortly after the introduction of sulfapyridine reports began to appear concerning certain toxic manifestations. These were concerned for the most part with effects on the hematopoietic system and on the urinary tract. Lloyd, Erskine and Johnson<sup>14</sup> noted some depression of the neutrophils following administration of sulfapyridine to patients with gonorrhea, and later Coxon and Forbes<sup>5</sup> reported the first case of agranulocytosis. Many clinical reports followed. Wien<sup>26</sup> noted no change in the blood picture of rats given as much as 4 gm. per kilo daily for 2 weeks in the form of an aqueous suspension given orally. Toomey<sup>23</sup> found that a definite anemia developed in monkeys given sulfapyridine; no details are given.

Southworth and Cooke<sup>21</sup> were the first to report effects on the urinary tract in man. These, which included, in 3 cases, hematuria, albuminuria, crystals of the drug in the urine, renal colic, anuria lasting for 14 hours, and nitrogen retention, ceased when administration of sulfapyridine was stopped. Snapper, Liu, Chung, Yü



and Sun reported 4 cases of hematuria, 2 with renal colic, following treatment with sulfapyridine.<sup>20</sup> One case died and at autopsy a stone consisting of 55.3% acetyl-sulfapyridine and 1.9% sulfapyridine was found. Stokinger<sup>22</sup> found that crystals of acetyl-sulfapyridine appeared in the urine of the rabbit and man following ingestion. Antopol and Robinson<sup>1</sup> administered sulfapyridine to monkeys, rabbits and rats. Single large doses or repeated smaller doses gave rise to uroliths of acetyl-sulfapyridine. Thus 0.25 gm. per kilo in monkeys, 10-15 gm. per kilo in rabbits, and 5 gm. per kilo in rats given daily for 10 days produced uroliths. With single large doses crystals appeared in the urine in a few hours. Within 24 hours calculi appeared in the bladder; ureters and renal pelves showed dilatation, or masses of crystals filled the pelvis and extended into the medulla of the kidney. The organs were large and edematous and occasionally showed pyelonephritis. Gross, Cooper and Lewis<sup>8</sup> studying rats killed by treatment with sulfapyridine found dilatation of ureters and renal pelves and large soft kidneys. Concretions were frequently present producing more or less complete urinary obstruction and contained 6.4% sulfapyridine and 64.1% acetyl-sulfapyridine. Toomey,<sup>23</sup> autopsying monkeys given sulfapyridine found blood and crystals in the urine, concretions in bladder, ureters and renal pelves, dilatation of the pelves, swollen kidneys and pyelonephritis. Molitor and Robinson<sup>17</sup> gave sodium sulfapyridine orally to mice, rats, rabbits and monkeys as a 10% aqueous solution (pH 11.4). Single doses of 3-4.5 gm. per kilo produced gastric irritation in mice, rats and rabbits, and uroliths in rats and rabbits. When given daily for 10 days, 0.25 gm. per kilo produced gastric irritation and uroliths in monkeys and 2 gm. per kilo had the same effect in rats. Oral or intravenous administration of acetylated sodium sulfapyridine produced uroliths in mice, whereas uroliths were not found after the administration of the non-conjugated drug.

Wien<sup>26</sup> found that daily oral administration of 4 gm. per kilo of an aqueous suspension of sulfapyridine to rats for 2 weeks produced a retardation of the growth curve. One gram per kilo had no such effect.

Wien<sup>26</sup> also noted that the spleen in his rats was normal, and Johannsen and St. George<sup>11</sup> found no gross or histological lesions in the lungs, heart, liver, kidneys or spleen of mice receiving lethal or sublethal doses of sulfapyridine.

A brief account of pathologic studies in monkeys, rats and mice following prolonged administration of sulfathiazole and sulfapyridine has been given elsewhere.<sup>19</sup> Cooper, Gross and Lewis<sup>4</sup> have noted that sulfathiazole and sulfamethylthiazole, like sulfapyridine, produce renal concretions in rats.

**Technique.** *Mice.* Sulfathiazole and sulfapyridine were administered to Swiss mice, weighing between 11 and 20 gm., either at 1% or 2% in the standard Sherman dry diet.<sup>3,13</sup> There were 22 animals on each 1% diet

and 30 on each 2% diet. The feeding of the drug was continued for 4 weeks. It was found that, as others had shown,<sup>3,13</sup> the mice ate the drug diet mixture almost continuously. Consumption reached a peak around midnight and fell to a low level at 6 o'clock in the morning. After the first 2 days, during which the mice ate relatively poorly, the consumption of food was equivalent to that of the Sherman diet without drug. The only exception to this was in the case of the 2% sulfathiazole diet. Here the consumption of drug was more irregular and half of the mice ate less on this diet than on any other. In all cases, save one, it is to be noted that the latter were those that succumbed early to the toxic effect of the 2% sulfathiazole diet and part, if not all, of their small food consumption must be ascribed to anorexia. Mice receiving the diet containing 1% sulfathiazole consumed on an average 2.38 gm. of drug daily per kilo of starting weight (variation 1.77 gm. to 3.09 gm.). On 2% sulfathiazole diet the average amount consumed daily was 2.6 gm. of drug daily per kilo of starting weight (variation 1.03 gm. to 4.9 gm.). For 1% sulfapyridine diet the average was 2.26 gm. of drug daily (variation 1.65 gm. to 2.96 gm.). On the 2% sulfapyridine diet the figures were 3.37 gm. per day average (variation 2.8 gm. to 4.17 gm.).

*Rats.* In groups of 18, rats were administered the two drugs incorporated with the standard S-50 dry diet as 0.5% or 1%. S-50 diet consists of: Whole wheat, 29%; yellow corn, 30%; milk powder, 21%; linseed meal, 7%; cod-liver oil, 1%; meat scrap, 10%; alfalfa, 2%.

Food consumption, and hence amount of drug eaten, was not measured continuously but was determined twice at an interval of 1 month. After the rats had been on the diets for about 2 weeks and were then approximately 37 days old, the average amounts of drug eaten per kilo body weight per 24 hours were 0.47-0.48 gm. for 0.5% sulfathiazole, 0.62-0.75 gm. for 1% sulfathiazole, 0.41-0.43 gm. for 0.5% sulfapyridine, and 0.68-0.72 gm. for 1% sulfapyridine. One month later after the rats had grown considerably, the consumptions of drug, in terms of amounts eaten per kilo of body weight per 24 hours, were 0.26 gm. for 0.5% sulfathiazole, 0.55-0.64 gm. for 1% sulfathiazole, 0.26-0.31 gm. for 0.5% sulfapyridine, and 0.53 gm. for 1% sulfapyridine.

*Monkeys.* Two experiments were run with monkeys. In the first case the animals were given daily for 14 days 0.4 gm. of sulfapyridine or sulfathiazole per kilo of initial body weight. The drugs, as a 10% suspension in 5% gum acacia, were given once a day by means of a stomach tube. In this series there were 3 monkeys given sulfathiazole (weights from 3.4 to 4.7 kilos) and 3 given sulfapyridine (weights from 2.5 to 4.3 kilos). In the second series the only difference was that medication was continued for 21 days. In this case there were 4 animals receiving sulfathiazole (weights from 2.4 to 4.3 kilos) and 4 receiving sulfapyridine (weights from 3.0 to 4.7 kilos).

*Results. Mice.* Mice receiving either dose of sulfapyridine or the lower dose of sulfathiazole remained well throughout the 4-week period. Of those receiving the diet containing 2% sulfathiazole, 77% died. Deaths began on the 3rd day, 13% were dead by the end of the 5th day, and 70% by the end of the 20th day. The mice which survived on the 2% sulfathiazole diet often were those which consumed the food most heartily. Thus the average amount of diet consumed daily by these survivors was 3.29 gm. per kilo of initial body weight and the amounts varied from 2.34 to 4.9 gm.

All mice which survived were killed at the end of 4 weeks and autopsied. Those dying during the test period (2% sulfathiazole)

were also autopsied. No mice receiving either dose of sulfapyridine showed any gross pathologic changes. In those mice receiving 1% sulfathiazole the only gross pathologic change noted was that 13% showed a very small dark spleen and in 61% this change was also present though to a lesser degree. In the survivors on the 2% sulfathiazole diet the only changes noted in the gross were very small spleens in 2 instances and large pale kidneys in 2 instances. In those animals on the 2% sulfathiazole diet which died, no changes were noted until the 4th day. On that day and subsequently gross changes were seen in spleen and genito-urinary tract. The spleen was dark and either small or very small in 65%. The kidneys were large and pale in 45% and there was often definite hydronephrosis (Fig. 1). Concretions were found in the pelvis of the kidney or in the bladder in association with hematuria in 25%. These concretions when analyzed yielded about 25% free and 75% conjugated sulfathiazole.

Microscopically, those mice receiving 1% sulfapyridine diet showed no abnormalities in lungs or spleen. The livers of all mice in this group showed cloudy swelling which was very marked in half the animals (Fig. 2). The change in the early stages was in the center of the lobules. In 1 case there was some fatty infiltration. A few mice on this diet showed slight dilatation of the convoluted tubules of the kidney. These dilated tubules occasionally contained debris or even cellular casts.

On the 2% sulfapyridine diet lungs, spleen and central nervous system were normal microscopically. In the liver the same changes were seen as appeared in mice on 1% sulfapyridine, except that in 1 case a few foci of necrotic cells were found (Fig. 3). In the kidney changes were similar to those found on the 1% diet.

In those mice receiving 1% sulfathiazole the lungs were normal. In the spleen microscopic changes were found in 41%. These were present only in the Malpighian corpuscles. In a few cases germinal centers were hyperplastic. In others they were smaller than normal, appeared disorganized, or had even disappeared and pyknotic cells were present. In some cases, moreover, the small lymphocytes of the mantle zone had disappeared or decreased in number. In the kidney the changes seen were similar to those seen in mice receiving 1% or 2% sulfapyridine diets. They were perhaps slightly more extensive and in 1 case many of the convoluted tubules were lined with hyaline necrotic cells. Changes in the liver were similar to those seen with sulfapyridine.

In the survivors on the 2% sulfathiazole diet the lungs and central nervous system were normal. Lesions in the spleen, found in 50%, consisted in disorganization of the germinal centers with pyknosis of many of the lymphoblastic cells and their ultimate disappearance. (Figs. 4 and 5.) In the liver there was cloudy swelling as with sulfapyridine (Fig. 6). In 2 cases fatty infiltration was noted

PLATE I

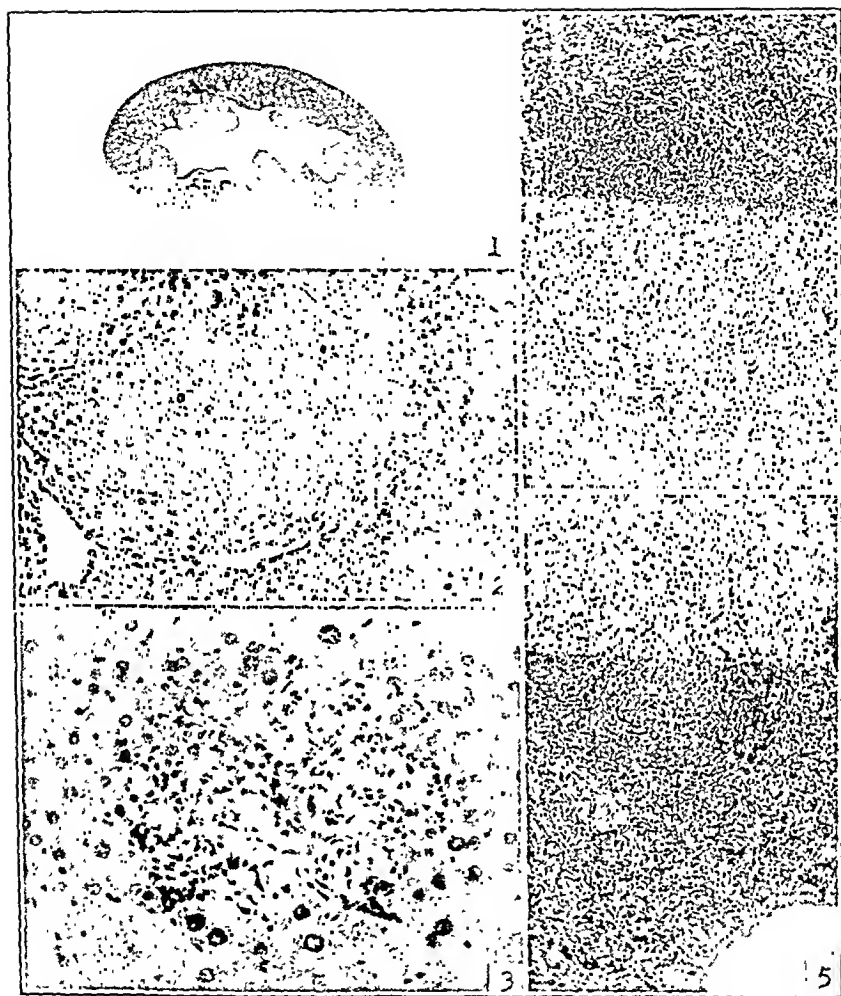


FIG. 1.—Sulfathiazole. Mouse kidney showing hydronephrosis. ( $\times 7$ . H. and E.)

FIG. 2.—Sulfapyridine. Mouse liver showing cloudy swelling. ( $\times 110$ . H. and E.)

FIG. 3.—Sulfapyridine. Mouse liver showing necrosis and leukocytic infiltration. ( $\times 260$ . H. and E.)

FIG. 4.—Normal mouse spleen showing Malpighian corpuscle. ( $\times 110$ . H. and E.)

FIG. 5.—Sulfathiazole. Mouse spleen showing alterations in the germinal center of a Malpighian corpuscle and loss of lymphocytes from the marginal and mantle zones. ( $\times 110$ . H. and E.)

PLATE 2

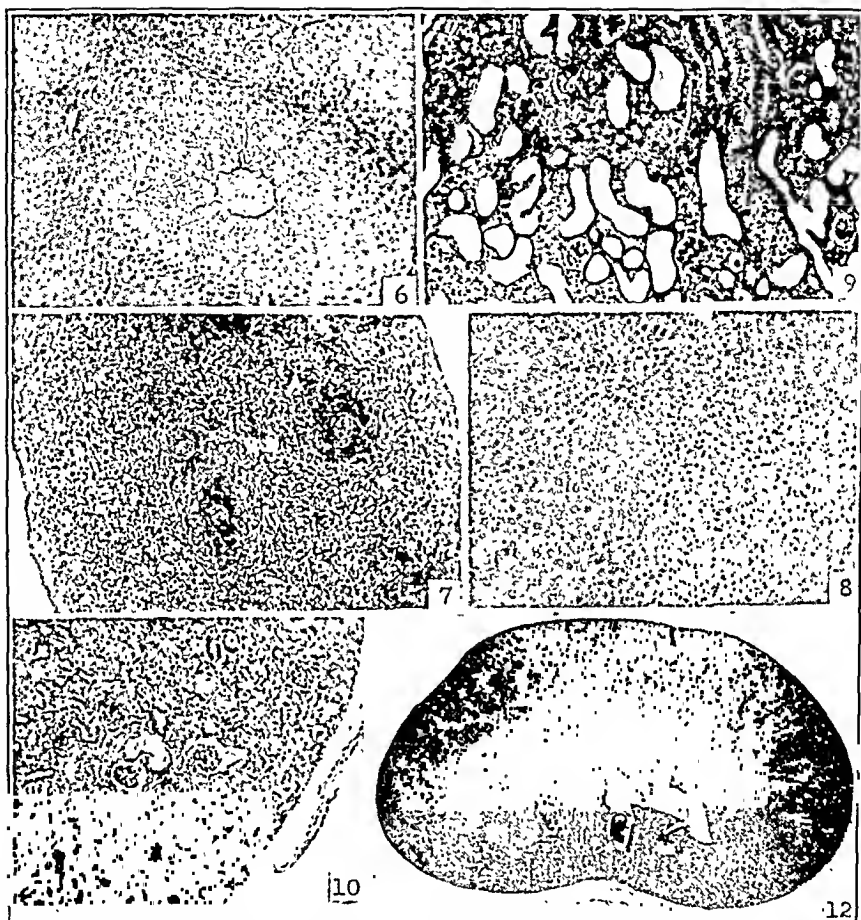


FIG. 6.—Sulfathiazole. Mouse liver showing cloudy swelling. ( $\times 110$ . H. and E.)

FIG. 7.—Sulfathiazole. Mouse spleen showing disappearance of all lymphoid elements from the Malpighian corpuseles. The entire width of the spleen appears in the illustration demonstrating the decrease in size of the organ. ( $\times 110$ . H. and E.)

FIG. 8.—Sulfathiazole. Mouse liver showing area of necrosis. ( $\times 110$ . H. and E.)

FIG. 9.—Sulfathiazole. Mouse kidney showing dilatation of tubules in the cortex. ( $\times 110$ . H. and E.)

FIG. 10.—Sulfathiazole. Mouse kidney showing dilatation of glomerular capsules and tubules with albuminous casts. ( $\times 110$ . H. and E.)

FIG. 12.—Sulfathiazole. Rat kidney showing maximum change produced. Slight dilatation of the renal pelvis. ( $\times 7$ . H. and E.)

PLATE 3

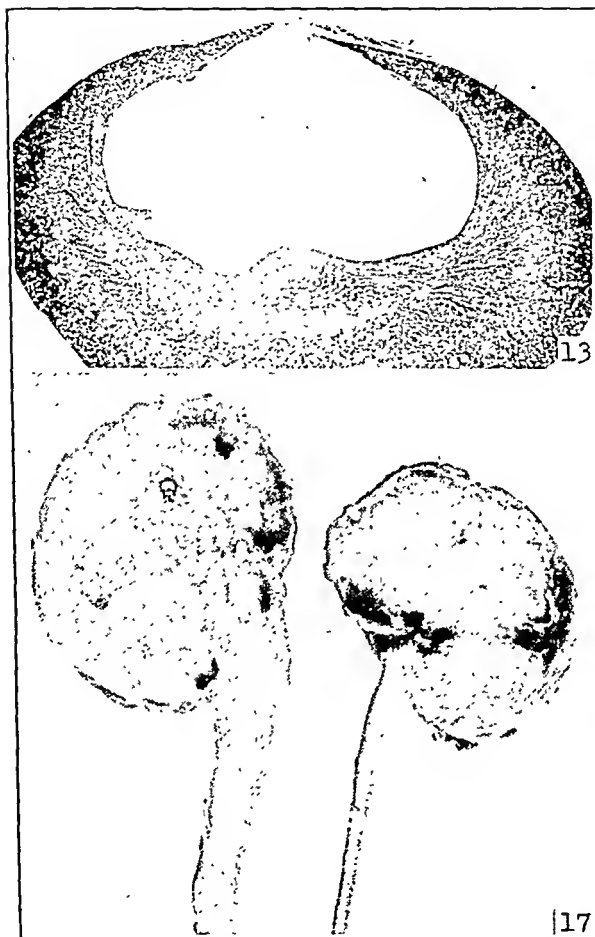


FIG. 13.—Sulfapyridine. Rat kidney showing hydronephrosis with compression of the organ and dilatation of tubules in cortex and medulla. ( $\times 7$ . H. and E.)

FIG. 17.—Sulfapyridine. Monkey 49. Kidney. Hydronephrosis and hydro-ureter on the right side.

PLATE 4

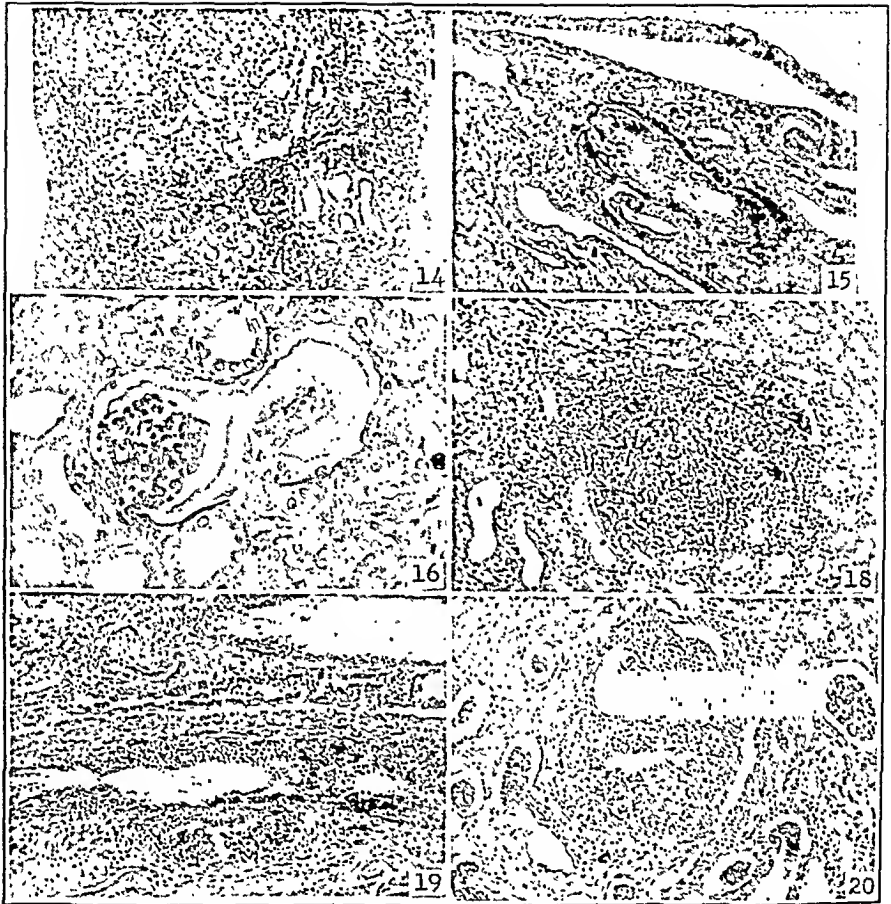


FIG. 14.—Sulfapyridine. Rat kidney showing the total width of the organ. Some tubules dilated, others collapsed and surrounded with scar tissue. ( $\times 110$ . H. and E.)

FIG. 15.—Sulfapyridine. Rat kidney showing the outline of crystals in a tubule and surrounding leukocytic infiltration. ( $\times 110$ . H. and E.)

FIG. 16.—Sulfapyridine. Monkey kidney showing albuminous cast filling the glomerular capsule and commencement of the tubule. ( $\times 260$ . H. and E.)

FIG. 18.—Sulfapyridine. Monkey kidney showing leukocytic infiltration in and around tubules forming an abscess. ( $\times 110$ . H. and E.)

FIG. 19.—Sulfathiazole. Monkey kidney showing the outline of crystals in tubules and surrounding leukocytic infiltration. ( $\times 110$ . H. and E.)

FIG. 20.—Sulfathiazole. Monkey kidney showing leukocytes in and around the tubules. ( $\times 110$ . H. and E.)

at the periphery of the lobule and in 2 others, small areas of hyaline necrosis with cellular infiltration were seen. In half of the cases very little was to be seen in the kidney except dilatation of the convoluted tubules which contained débris or a few casts. In the other half the changes were more extensive. Both the convoluted, and in 2 cases also the collecting, tubules were greatly dilated and contained hyaline and cellular casts. In 1 case there were marked changes in the cells lining the convoluted tubules which amounted in places to complete necrosis. In the same kidney blood was present both in Bowman's capsule and in the convoluted tubules. In another case it was possible to see in the collecting tubules angular outlines obviously indicating where crystals of drug had been. Such tubules were surrounded with leukocytes.

In those mice which succumbed to the 2% sulfathiazole diet similar microscopic changes were observed. In 1 case there was a terminal pneumonia but lungs from the others were normal. No lesions were observed in the brain or spinal cord. The changes in the spleen were more marked. In most instances not only had the germinal centers of the Malpighian corpuscles disappeared completely but, in addition, the mantle and marginal zones of lymphocytes had disappeared, leaving nothing but foci of collapsed splenic stroma (Fig. 7). The changes in the liver of those that died were similar in type to those seen in the mice killed after 28 days but were less in degree. In 1 case, however, there were two large areas of necrosis (Fig. 8).

All mice dying after the 3rd day showed lesions of the kidney. These changes were the same as those seen in the mice killed after 28 days. Dilatation was not confined to the convoluted tubules (Fig. 9) but in 2 cases involved the glomerular spaces (Fig. 10). Cytoplasmic changes in the cells of the cortical tubules were also more frequent. Blood was seen in Bowman's capsule and the convoluted tubules in 1 case and the outlines of crystals in the collecting and convoluted tubules in another.

*Rats.* All rats survived for the 57-day period of the test. The gain of weight, however, was significantly less in the rats receiving sulfapyridine. Rats receiving  $\frac{1}{2}\%$  sulfathiazole in the diet gained weight equally with the controls (Chart 11). At the end of the 57 days complete blood counts were made on all rats, which were then killed. All blood counts were normal. At autopsy in those animals receiving  $\frac{1}{2}\%$  sulfathiazole, 2 out of 15 showed fine yellow streaks in the medulla of the kidneys. The remainder were normal. Of 18 animals receiving 1% sulfathiazole 5 showed similar changes in the kidneys. Only 3 of 17 rats receiving  $\frac{1}{2}\%$  sulfapyridine were normal in the gross. One of the others showed only what appeared to be deposits of crystals in the medulla of the kidneys. The others showed concretions in bladder, ureters or pelvis, or all three, with hydroureter and hydronephrosis in 10 cases, and marked hem-



aturia in 1. Of rats on 1% sulfapyridine 5 out of 16 were normal. The others showed concretions in bladder, ureters or pelvis, or all three sites, with hydroureter and hydronephrosis in most cases.

Microscopically, in the rats on  $\frac{1}{2}$ % sulfathiazole the liver, spleen and bone-marrow were normal. The kidney was also normal except in two of those examined. In one of these there was dilatation of all renal tubules and in the other, slight dilatation of the renal pelvis (Fig. 12) and more marked dilatation of all tubules. These tubules contained a few casts and some débris; in a few places cytoplasmic changes were seen in the lining cells. On the 1% sulfathiazole diet liver, spleen and bone-marrow again were normal. The kidney changes resembled those seen in the group on  $\frac{1}{2}$ % sulfathiazole.

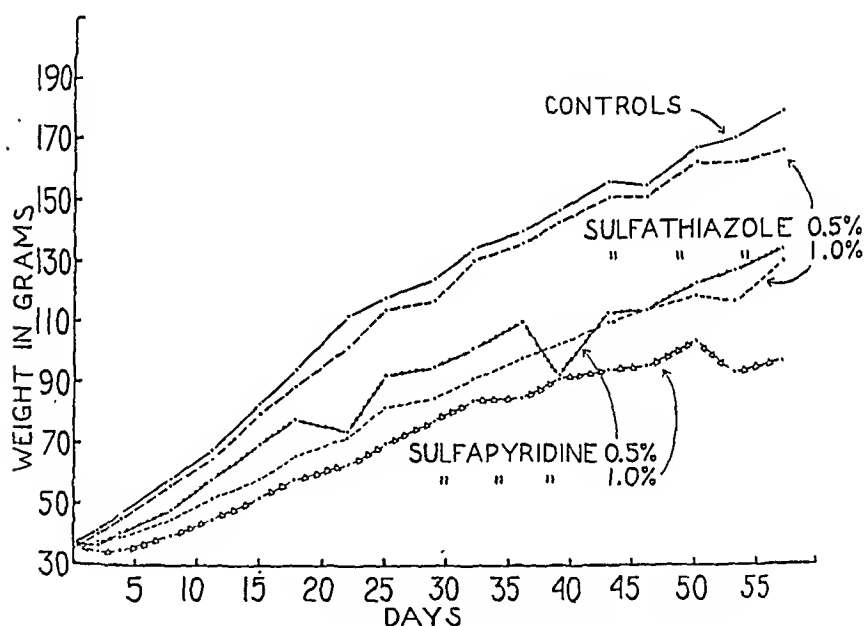


CHART 11.—Growth curves of groups of rats receiving control diet and diets containing sulfapyridine or sulfathiazole. (Reproduced from Van Dyke, H. B., Greep, R. O., Rake, G., and McKee, C. M., *Proc. Soc. Exp. Biol. and Med.*, 42, 410, 1939.)

The liver, spleen and bone-marrow were normal in animals receiving either  $\frac{1}{2}$ % or 1% sulfapyridine in their diet. The changes in the kidneys were similar in the two groups. There was marked dilatation of the pelvis of the kidneys (Fig. 13) in all but 1 case and in most instances this hydronephrosis had produced in turn collapse and destruction of most of the tubules and glomeruli and their replacement by scar tissue (Fig. 14). Those tubules which were not collapsed were dilated and contained débris, casts and the outlines of crystals with surrounding leukocytic infiltration (Fig. 15). The lining cells were usually necrotic. In 1 case the tubules contained blood.

*Monkeys.\** In the 3 monkeys receiving sulfathiazole for 14 days 1 showed a 15% drop in hemoglobin and all showed some degree of leukopenia. The urine and the non-protein nitrogen in the blood remained normal. There was no loss of weight. At autopsy apart from tuberculosis the only change was microscopic dilatation of the convoluted tubules with a few casts and débris in 2 animals.

In the animals receiving sulfathiazole for the longer period, 3 survived the 21 days. Of these 2 remained well throughout the period and the third showed some degree of leukopenia. At autopsy apart from tuberculosis the only changes were renal and resembled those in monkeys receiving sulfathiazole for 14 days. The fourth monkey in this group remained normal until the 17th day when albumin, red cells and crystals were found in the urine. Next day the monkey was dead. It showed 10% loss of weight. There were crystals in the bladder and a concretion impacted in the left ureter with dilatation of ureter and renal pelvis above. Both kidneys were filled with crystals which delineated the medullary rays and spotted the cortex. Microscopically, many tubules showed outlines of crystals (Fig. 19). Around such tubules and elsewhere were dense leukocytic infiltrations (Fig. 20).

All of the 3 animals receiving sulfapyridine for 14 days showed considerable leukopenia. The non-protein nitrogen of the blood rose in all, the highest figures being 260, 90 and 63 mg. per 100 cc., respectively. All 3 showed albumin and crystals in the urine and one in addition showed blood. The weight loss was 21%, 10% and 8% respectively. At autopsy, apart from tuberculosis, concretions were present in renal pelves, ureters or bladder (in 1 case in all three). Above the ureteral stones there were hydronephrosis and hydroureter (Fig. 17). Microscopically, tubules and glomerular capsules were dilated and contained albuminous fluid (Fig. 16), blood, casts and débris.

All of the 4 monkeys receiving sulfapyridine for 21 days showed leukopenia. In 1 the hemoglobin decreased 10%. In 3 the non-protein nitrogen was increased, the highest figures being 68, 62 and 108 mg. per 100 cc. Crystals and albumin appeared in the urine of all animals and blood in 2. The loss in weight was 6%, 12%, 14% and 24%. At autopsy one animal showed no changes in the gross and microscopically showed only dilatation of convoluted tubules with a few casts and débris. A second showed moderate bilateral hydroureter and microscopic changes somewhat more advanced than the first. In the other 2 there were ureteral concretions, hydroureter and hydronephrosis with pyelonephritis in 1 case. Microscopically, the tubules and glomerular capsules were dilated and contained albuminous fluid, casts and débris. There

\* Since all monkeys were to be killed at the end of the experiment animals were chosen which appeared to have tuberculosis and most animals showed tuberculous lesions at autopsy.

were necrosis and other changes in the cells of the convoluted tubules. The pyelonephritis was represented by numerous abscesses in cortex and medulla (Fig. 18).

**Discussion.** Although sulfapyridine given as 1% or 2% of the diet did not appear to affect the mice adversely, microscopic examination showed that both drug concentrations had some effect on liver and kidneys. Similar slight changes in liver and kidneys were noted in mice given 1% sulfathiazole, and these animals in addition showed changes in the spleen resembling those described in certain other intoxications.<sup>6</sup> With 2% sulfathiazole diet, serious effects occurred. Deaths began as early as the third day and during the 28-day period of observation 77% of the animals died. These deaths seemed to be due chiefly to the effect on the genito-urinary system and great individual variation, perhaps in the degree of conjugation of the drug, was found. In half of the mice which survived the 28-day period little was seen in the kidney but the changes in spleen and liver resembled those seen in the animals that died. None of these changes were due to post-mortem autolysis since similar changes were found in surviving mice whose organs were fixed immediately. It should be noted that besides those renal changes due to the mechanical effect of the crystals or of concretions of these crystals, there appeared to be primary damage to the glomeruli as shown by hemorrhage at this point, and to the cytoplasm of the cells of the convoluted tubules.

In rats, in contrast to the mice, sulfathiazole was considerably less toxic than sulfapyridine. This was shown first by the growth curves (Chart 11). The amounts of drug consumed daily per kilo of initial weight did not differ significantly from one drug to the other. Only the genito-urinary tract showed lesions. Here sulfathiazole at either dose level produced very slight changes but both 0.5% and 1% sulfapyridine produced marked alterations. Recent experiments which have been performed in this laboratory suggest that the rate of metabolism of sulfathiazole in rats is so rapid and the sojourn of the drug in the blood so short that the blood level of rats receiving the 1% sulfathiazole diet will approximate that of rats receiving 0.5% sulfapyridine. This blood level of sulfathiazole, however, probably is not associated with genito-urinary lesions as frequently as an equal blood level of sulfapyridine. Metabolic studies are in progress to determine the total amount of drug passed through the kidneys at each dose of the two drugs. In the case of rats on sulfapyridine, as with mice on sulfathiazole, there appeared to be primary damage to the glomeruli and cells of the convoluted tubules quite distinct from those changes due to the mechanical effects of the crystals. It would appear that the different effect seen in mice and rats represents variation in species susceptibility. When the drugs are administered by mouth sulfapyridine is twice as toxic in rats as shown by the effect on the growth curve and more than twice

as toxic when the effect on the genito-urinary tract is considered. In the mice, on the other hand, when sulfathiazole is administered at levels above those necessary for therapeutics (*i. e.*, 2% in the diet), this drug produces marked genito-urinary changes and sulfapyridine produces none.

In monkeys the drugs were administered only once a day by stomach tube. It is realized that under these circumstances the blood concentration will be maintained at a more constant and higher level in the case of sulfapyridine than in that of sulfathiazole.<sup>24</sup> It is to be noted that the marked effect of either drug is on the genito-urinary tract and it would seem logical to suppose that the drug which was excreted more rapidly and in higher concentration through the kidneys, namely sulfathiazole, would produce the greatest effect or at least one not less than that of sulfapyridine. Such actually is not the case. In only 1 of 7 monkeys on sulfathiazole was there any effect on the genito-urinary tract and this was acute rather than chronic with steady rise in the non-protein nitrogen. With sulfapyridine, on the other hand, 6 out of 7 animals showed marked mechanical alterations in the genito-urinary tract and also primary renal damage. In every case this was accompanied by a rise in the non-protein nitrogen, often to high figures. The monkey dying from the effect of sulfathiazole and one of those on sulfapyridine showed widespread pyelonephritis. Unfortunately no cultures were taken but there is reason to believe that they would have proved sterile. These cases appeared to be merely an extension of what was seen in the rats and mice, namely an infiltration of leukocytes around any tubules or groups of tubules containing crystals of the drug. In addition to the genito-urinary changes it should be noted that 1 monkey on sulfathiazole (the animal which died) and 4 on sulfapyridine showed a loss of weight of greater than 10% during the experiment. In addition, 4 monkeys receiving sulfathiazole and all of those receiving sulfapyridine showed a steady decrease in the number of neutrophils in the blood which seemed to be significant.

**Summary.** 1. Sulfathiazole when given as 2% of the diet killed 77% of mice during a 4-week period and produced lesions chiefly in the spleen and genito-urinary tract. Sulfapyridine was not lethal and produced fewer pathologic changes.

2. In rats sulfapyridine was twice as toxic as sulfathiazole as shown both by the effect on the growth curve and by the lesions produced in the genito-urinary tract.

3. In monkeys receiving a single daily dose sulfapyridine was more toxic than sulfathiazole as shown by the lesions in the genito-urinary tract and, to a lesser extent, by loss of weight and leukopenia.

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## PERIPHERAL NEUROPATHY AND TOXIC PSYCHOSIS WITH CONVULSIONS DUE TO SULFAMETHYLTHIAZOLE.

### REPORT OF A CASE.

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THE toxic reactions caused by sulfamethylthiazole are similar in general to those of sulfanilamide and sulfapyridine. Thus, drug fever, dermatitis, granulocytopenia and hemolytic anemia have been encountered at Cleveland City Hospital following the use of sulfamethylthiazole. These reactions have not differed in any important detail from those described for sulfanilamide<sup>2</sup> and sulfapyridine.<sup>1</sup> Crystals of the drugs have frequently been found in the urine of patients receiving sulfamethylthiazole, as happens in patients receiving sulfapyridine,<sup>4</sup> and in several patients, hematuria has resulted.

Peripheral neuropathy, another complication which has been ascribed to sulfanilamide and certain of its allied compounds,<sup>3,6,7</sup> also has been encountered following the use of sulfamethylthiazole.<sup>8</sup> In one instance at Cleveland City Hospital the peripheral neuropathy was associated with a toxic psychosis. The character of the toxic reaction in this case was unusual enough to merit detailed consideration.

**Case Report.** E. K., a negro woman, aged 37, was admitted to Cleveland City Hospital, March 6, 1940. She had been in good health until March 1, when she had a severe chill followed by pain in the right side of the chest. Subsequently she became feverish and short of breath and coughed up sputum streaked with blood. She never had had convulsions and was not an alcoholic.

Examination showed an obese, acutely ill, moderately dyspneic negress. There was clinical and roentgenologic evidence of pneumonia involving the upper and middle lobes of the right lung. The temperature was  $40.1^{\circ}\text{C}$ . ( $104.2^{\circ}\text{F}$ .), the pulse was 145 and the respiratory rate 45 per minute. Otherwise the physical examination was negative.

A Type XIV pneumococcus was found in both sputum and blood. The leukocytes numbered 9300 per c.mm., 82% being neutrophils. The red blood cell count was 4,000,000 and the hemoglobin was 10 gm. per 100 cc. Urinalysis revealed albumin, Grade 2. The slide test for syphilis (Kline) was positive; the Wassermann test was negative.

An initial dose of 4 gm. (60 gr.) of sulfamethylthiazole was given, with 1 or 2 gm. (15 or 30 gr.) every 4 hours thereafter. See Chart 1 for the exact amounts.

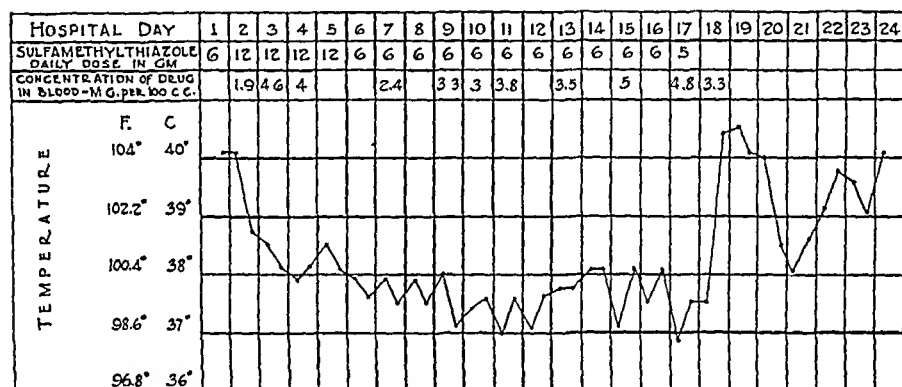


CHART 1.—Doses of sulfamethylthiazole, concentration of the drug in the blood, and temperature.

Four hours after admission, reexamination showed the cardiac mechanism to be auricular fibrillation. Digitalis was given. In 36 hours the mechanism reverted to normal, and the use of digitalis was discontinued.

The patient improved slowly. There was no growth in the blood cultures taken on the second, third, fourth and sixth hospital days. The temperature fell gradually by lysis but did not become normal and since resolution of the pneumonic process was occurring slowly, chemotherapy was continued. The blood level of sulfamethylthiazole averaged 3.6 mg. per 100 cc. of blood (Chart 1).

Despite the fact that thiamine chloride was being administered intravenously and intramuscularly, on the seventeenth hospital day there was definite tenderness and hyperesthesia of the legs, which was considered to be indicative of early peripheral neuropathy. The use of sulfamethylthiazole was stopped immediately. The patient was oöperative and mentally clear at this time.

The next morning the patient had two generalized convulsions, each of which lasted about 3 minutes, following which she was unresponsive, agitated, resistive, delirious and required restraint and intravenous sedation. As far as could be determined, neurologic and general physical examination was negative. A lumbar puncture was done and the spinal

fluid pressure was found to be normal. The fluid was clear and contained no cells. The Wassermann reaction of the spinal fluid was negative. That afternoon the temperature rose to 40° C. (104° F.) and her condition was poor.

During the following 3 days the patient had 12 generalized convulsions. She was unresponsive, stuporous and in a critical condition. No abnormal physical or neurologic findings could be demonstrated. A film of the chest showed almost complete resolution of the pneumonic process. Another lumbar puncture was done and again the spinal fluid was found to be normal. The blood urea nitrogen was 32.6 mg. per 100 cc. of blood. The white blood cell count was 12,000 and the red blood cell count was 4,200,000. Urinalysis was negative except for a small amount of albumin. The patient became increasingly stuporous during the next 2 days and died on March 29, on the twenty-fourth hospital day.

*Autopsy.* (No. 13167, performed by Dr. K. H. Kemp, 1½ hours after death.) The lungs showed no evidence of pneumonia. There was bronchiectasis and bronchitis in the upper lobe of the right lung. The alveoli of the middle and lower lobes of the right lung contained blood, apparently of rather recent origin. There were considerable edema and a few small areas of hemorrhage in the left lung. The heart was normal. The abdominal viscera showed severe cloudy swelling. The brain was normal grossly and microscopically.

*Comment.* The clinical and autopsy findings adequately establish the fact that this patient died of a toxic psychosis. Only two drugs, thiamine chloride and sulfamethylthiazole, need to be considered as possible causative agents. Thiamine chloride cannot be incriminated, as massive doses of this drug have not caused toxic symptoms. On the other hand, it is reasonable to ascribe the toxic reaction to sulfamethylthiazole, especially since the sulfanilamide radicle has been known to cause toxic psychoses. Convulsions caused by sulfanilamide have not been reported<sup>5</sup> and in this respect the case is noteworthy. The peripheral neuropathy can be attributed to no other cause than the sulfamethylthiazole and is additional evidence of the toxicity of the drug to this particular patient.

*Summary.* Experience at Cleveland City Hospital indicates that in general the toxic reactions of sulfamethylthiazole resemble those previously described for sulfanilamide and its allied compounds. One case at Cleveland City Hospital has been exceptional and has demonstrated a hitherto unreported reaction. In this instance peripheral neuropathy appeared while the patient was receiving sulfamethylthiazole. The use of the drug was stopped but shortly thereafter the patient suffered a violent toxic psychosis with convulsions and died.

Sulfamethylthiazole was available for study through cooperation with the Medical Research Division of the Winthrop Chemical Company.

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## SULPHAPYRIDINE IN THE TREATMENT OF GONOCOCCAL INFECTIONS AFTER SULPHANILAMIDE FAILURE.

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THE therapy of gonococcal infections has undergone great change and improvement since the introduction of the sulphanilamide class of drugs. The relative merits of the various modifications, however, still remain to be evaluated for different diseases.

In a previous study<sup>1</sup> of the hospital treatment of gonorrhea with sulphanilamide, we found that it was promptly effective in 76% of 298 patients. The failure patients we considered under three different groups: 1, Those who did not respond to sulphanilamide in adequate doses; 2, those inadequately treated as out-patients; 3, self treatment from irresponsible drug stores.

Groups 2 and 3 received an adequate course of sulphanilamide therapy after admission. However, it has been our experience that these patients are not responsive to further sulphanilamide therapy. Certain few individuals appear to change and excrete this drug too rapidly to secure clinical effect. Prolonged inadequate dosage appears to raise the resistance of the patient's infection towards the drug. Several theories as to the site and manner of action of the sulphanilamide chemicals have been expounded in the literature. It is not the purpose of this report to discuss them.

To evaluate the allied drug sulphapyridine in the sulphanilamide failure patients, 100 seafaring men, between the ages of 20 and 40 in good physical condition were selected. All of these patients had been adequately treated with sulphanilamide.

**Method.** The initial dose of sulphapyridine was 1 gm. every 4 hours day and night for 2 days, then  $\frac{1}{2}$  gm. every 4 hours day and night for 4 to 8 days, according to the patient's response.

The average number of days of treatment was 7. We did not correlate the concentration of the drug in the blood with the dosage in this investigation.

The fluid intake was limited to 1 quart per 24 hours. During the summer months  $1\frac{1}{2}$  quarts were allowed. When laxatives were necessary enemata or cascara sagrada were used.

The results of this treatment were 75% of cures in 100 patients who had failed upon sulphanilamide. In the successful cases the urethral discharge disappeared within 5 days after administration of sulphapyridine.

The criteria of cure was as follows: After the disappearance of the urethral discharge and the urine was clear by the 2-glass test.



the meatus was cleansed with soap and water. A curved sound was passed into the bladder. The pendulous portion of the urethra was massaged on the sound. The sound was withdrawn and the prostate was massaged. The urethro-prostatic secretion was examined by smear and culture.

If found to be negative for gonococci, the entire procedure was repeated after a 2-day interval. Three such negative reports were obtained before the patient's release.

The sounds were lubricated with sterile tragacanth jelly free of preservatives.

A slight serous "morning drop," a few fine shreds when both glasses of urine were clear were not construed as indicating failure if the other criteria of cure were present.

We are now using this drug for the routine hospital treatment of the gonococcal infections.

It has been more agreeable for the patients to take. The cyanosis is less. However, the nausea and malaise are quite constant for each patient. Numerous crystals are present in the urine, also red and white cells, and small amounts of albumin while the patient is under treatment. These urinary findings clear up after treatment without residual effects in our experience. We have encountered no alarming symptoms among many patients treated, exclusive of the above group of sulphanilamide failures. One individual, not in this group, developed a mild granulocytic leukopenia. He recovered promptly after the discontinuance of the drug.

However, we reiterate the opinion expressed in our article on sulphanilamide therapy, that this class of chemicals is not without danger if prescribed to patients who are not in the hospital or who are not under daily clinical observation.

The toxic symptoms of nausea and malaise may cause certain out-patients to discontinue the recommended amounts of drug, and thus result in failure of treatment.

Patients under therapy with sulphapyridine or sulphanilamide class of drugs should receive frequent blood counts to guard against granulocytosis.

**Conclusions.** 1. One hundred patients who had failed of cure on sulphanilamide therapy were treated with sulphapyridine.

2. Of these, 75 were cured in an average of 7 days.

3. Inadequate treatment with sulphanilamide raises the resistance of the patients' infection towards this drug.

4. Sulphapyridine has proved superior to sulphanilamide in the treatment of gonorrhea in our experience.

5. It is preferable to treat patients in the hospital to insure against untoward toxic effects and to assure correct and adequate dosage.

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## TREATMENT OF THE FALCIPARUM MALARIA OF DRUG ADDICTS.

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FALCIPARUM malaria is endemic in the drug addict population of New York City.<sup>1</sup> Since 1933, more than 200 such cases have been admitted to our wards in Bellevue Hospital. Epidemiologic,<sup>2a</sup> clinical,<sup>2b</sup> and laboratory<sup>3</sup> studies of these patients who have presented every clinical variety of falciparum malaria, have been reported elsewhere. Since the practise leading to the transmission of this disease—the common use of an apparatus for the administration of heroin intravenously—is becoming increasingly popular among drug addicts, it is likely that endemic foci will appear also in other cities. It seems desirable, therefore, to report our tried and satisfactory routine for the treatment of its various clinical forms.

In the early years of our experience with this disease, the mortality exceeded 50%. This was due, we now believe, to the following circumstances: first, that the patients presented themselves for treatment late in the course of the disease; second, that the medical staff often failed to establish the diagnosis within a few hours of the patient's admission; third, that the staff was not familiar with an effective method of treating the cerebral form of this disease. In recent years the mortality has fallen to about 10%. This has resulted, we believe, from the reversal of the above conditions. The object of this paper, therefore, is to describe that form of treatment which has been most effective in producing rapid recovery from the disease with the shortest possible period of hospitalization, reducing to a minimum the likelihood of relapse, and preventing the patient from becoming a public health menace. These objectives were accomplished by a combination of specific chemotherapy and supportive measures.

Chemotherapy consists of:

1. The destruction of asexual parasites, responsible for the disease in man, by the administration of quinine dihydrochloride intravenously, or atabrine orally, or both. Quinine dihydrochloride is given intravenously as an emergency measure, to establish immediately a high concentration of a plasmodicide in the blood of patients

showing involvement of the nervous system, or when vomiting or diarrhea exists. Atabrine is given after a satisfactory response to the emergency treatment with intravenous quinine has occurred. In the less severely ill patients, who do not exhibit cerebral or gastrointestinal signs or symptoms, atabrine is given in the first place, the intravenous therapy being omitted.

2. The destruction of sexual parasites, responsible for transmission of the disease via the mosquito, by the administration of plasmochin. This drug is given only as a gametocide after a clinical response to quinine and atabrine has been obtained, or to symptomless carriers of gametocytes.

Supportive therapy consists of combatting shock, dehydration, anemia, and hypoproteinemia by the restoration of fluids, salt, blood, and plasma proteins.

The application of these therapeutic principles to the various clinical forms of falciparum malaria in the drug addict will be described separately for each one.

*Cerebral Form.* In the presence of cerebral involvement as manifested by clouding of consciousness, severe headache, convulsions, or frank neurologic signs (such as pyramidal tract or posterior column signs, ocular palsies, rigidities, and other encephalopathic manifestations), quinine dihydrochloride is administered intravenously, in doses of 0.6 gm. in 10 cc. of physiologic saline solution, every 3 to 4 hours for at least 24 hours during the day and night. No effort is made to give food or drugs by mouth or stomach tube. From 2000 to 5000 cc. of fluids per day is given parenterally in the form of a 5% solution of glucose in physiologic saline, to which 10 mg. of thiamin chloride is added as a prophylaxis against vitamin B<sub>1</sub> deficiency. This is continued until urine specimens, obtained every 8 hours by catheter, are free from acetone and have a specific gravity of less than 1.015. If there is severe anemia or jaundice, or if the urine is bright red or brown and contains oxyhemoglobin or methemoglobin; if shock is present, or if the plasma proteins are low, 500 cc. of whole citrated blood is given as an infusion. This is repeated within 12 to 24 hours if evidence of marked hemolysis persists. If there is marked cyanosis, oxygen is administered by nasal catheter or mask. If there is no remission in the depth of the coma within 8 hours, 50 cc. of spinal fluid is withdrawn. Simultaneously, 50 cc. of a 50% glucose solution and 1 cc. of 1 to 10,000 adrenalin are given intravenously. This procedure may be repeated in 6 hours if no improvement in the clouding of consciousness is apparent. Dramatic recovery from severe coma or convulsions is brought about occasionally by this expedient.

When clinical improvement is noted, usually on the second day, the interval between intravenous injections of 0.6 gm. of quinine, is lengthened to 6 hours. If improvement continues, the intervals are lengthened to 8 hours on the third day, and to 12 hours on the fourth

day. The intravenous administration of quinine dihydrochloride is continued on the third and fourth days even though the patient looks and feels well and is able to take nourishment by mouth; it is limited to 4 days, however, even in severely ill patients.

As soon as the patient can take fluids by mouth he is encouraged to drink fruit juices and milk at frequent intervals. This nourishment is supplemented by semi-solid foods as soon as possible. No drugs are given by mouth and enemas are given every day. In order to avoid the intestinal or nervous complications of drug withdrawal, no attempt is made to withhold heroin or morphine, until the patient is convalescing from the falciparum malaria. The efficacy of treatment is judged, during this acute phase, by disappearance of the cerebral manifestations rather than by the temperature or the number of parasites found in the blood.

The next phase of treatment consists of giving atabrine, by mouth, in doses of 0.1 gm. three times daily for 7 days. At this time, when the patient is usually convalescent, a diet rich in calories and vitamins, supplemented by injections of liver parenterally, ferrous sulphate, and vitamin concentrates, is prescribed, and drug withdrawal is started. If, after 7 days of atabrine, gametocytes are found in the peripheral blood, plasmochin is given for 4 days in doses of 1 tablet of 0.02 gm. three times daily. The specific treatment for malaria is now ended. When heroin withdrawal is completed, the patient is instructed to return to a follow-up clinic for observation.

If, when admitted, the patient presents only a few or no neurologic signs, and only mild mental symptoms, such as moderate confusion, dullness, and apathy, the treatment after the first 24 hours need not be so vigorous as outlined. On the second day quinine may be given intravenously only every 8 hours and the administration of atabrine may be started on the third day, and continued for 7 days. In other respects the treatment is as outlined.

*Severe Gastro-intestinal Involvement.* A moderate number of individuals show evidence of severe intestinal localization of the infection in the form of intractable vomiting, often associated with jaundice, or severe diarrhea. In such cases the patient's stomach is lavaged and a purge given immediately following his admission to the ward, after which he is permitted to have nothing but cracked ice by mouth. Enemas are administered daily. During the first 2 or 3 days quinine dihydrochloride is administered intravenously and fluids parenterally as in the cerebral form. By the end of the second or third day the gastro-intestinal symptoms have, as a rule, disappeared. At this time atabrine by mouth is substituted for the quinine for a full week, and a low residue diet is prescribed and gradually increased in quantity. If gametocytes are present in the blood, plasmochin is given before the patient is discharged from the hospital.

*Blackwater Fever.* This syndrome, the result of intravascular corpuscular hemolysis, is characterized, in its early stage by malaise, chills, abdominal or loin pain, vomiting, shock, and dark red, brown, or black urine; later by fever, azotemia, oliguria to anuria, and jaundice. The signs and symptoms depend on the extent of the initial hemolysis and on whether the process recurs. Although blackwater fever is rare in New York, we have seen 2 cases in our series of drug addicts having falciparum malaria.

Treatment consists of the administration of whole blood, by means of a continuous drip infusion, until the emergency of shock and severe anoxemia has been overcome. This method can be employed only if large amounts of blood (1,000 to 5,000 cc.) are available. Otherwise direct transfusions of blood and infusions of 5% glucose in physiologic saline solution must be resorted to. Quinine is not given, but if numerous parasites are present in the peripheral blood, atabrine may be given in the dosage previously described. As a rule, however, this phase of the treatment may be postponed until the patient has recovered from the blackwater fever.

*Simple Malaria, Latent Cases, Gametocyte Carriers.* Drug addicts having malaria uncomplicated by severe nervous system or gastrointestinal involvement, or symptomless addicts discovered harboring asexual forms of plasmodia, are treated by the administration of atabrine in doses of 0.1 gm. by mouth three times daily for 7 days. At the termination of this period 0.01 gm. of plasmochin is given three times daily until gametocytes are no longer found in the circulating blood. The patient is kept at bed rest, intake of fluids is forced and a diet rich in calories and vitamins is given. Bowel hygiene should not be neglected. If the patient is anemic 0.3 gm. of ferrous sulphate is given three times daily. If, in a routine examination of a drug addict, only gametocytes of *P. falciparum* are found in the blood, 0.01 gm. of plasmochin is given three times daily until they disappear.

*Relapse and Reinfection.* Subsequent to their treatment and discharge from the hospital, several patients returned within a fairly short time showing symptoms of malaria, and parasites in their blood. It is difficult to accept the statements of drug addicts, but in 2 of our patients it seemed fairly certain that there had been no re-exposure. One of these had been transferred to another ward after his recovery from the malaria, and the relapse occurred less than 2 weeks after termination of the original treatment. This patient, however, had received only quinine. The second individual had been sent to a convalescent home in the country, and his relapse occurred within 3 weeks. This patient had been treated fully with quinine, atabrine, and plasmochin, and was free of malarial symptoms and parasites, and of evident symptoms of heroin addiction, when he left the hospital. There were no other known addicts at the country home where the patient was sent, and it seems fairly certain that this patient was not exposed to reinfection naturally or artificially. This case is of particular interest in view of the evi-

dence that the relapse rate following atabrine is less than that for quinine; and further, because relapse occurred in spite of intensive therapy. These cases emphasize the desirability of post-convalescent observation.

Many drug addicts resort to intravenous heroin administration after their recovery and discharge from the hospital. Some of our patients who returned with a second attack of acute malaria, admitted the common use of syringes with other addicts during the interval. As the immunity to malaria is extremely short, reinfection was undoubtedly the mechanism accounting for the recurrence of malaria in these cases. Ironically, a few of these addicts died during the second episode of the disease.

*Effects of Treatment.* It is difficult to evaluate the effects of treatment in falciparum malaria among drug addicts. Lower mortality rates in recent years may be ascribed to the fact that addicts as well as hospital physicians know of the disease. As a result, patients present themselves early for treatment often announcing the diagnosis. Seldom is the diagnosis missed even in the admitting office. Treatment, therefore, is instituted promptly, and blood smears are taken only to confirm the diagnosis. In spite of these factors there were six deaths in 35 cases admitted to our services during 1938. In 1939, however, there were only two deaths in 50 acute cases. This is still a high death rate, but compares favorably with the 50 to 75% mortality experienced during the first years after the cerebral form of the disease was recognized.

There is no intention of correlating mortality and treatment. We merely wish to point out that the disease, as it occurs in these addicts is a serious one, and all efforts should be directed towards early and intensive therapy. If because of inexperience or lack of facilities a diagnosis of malaria cannot be confirmed in an acutely ill drug addict, specific therapy should be given. Likewise in acutely ill patients having the telltale discolorations of drug administration over the antecubital veins, this diagnosis should be seriously considered and specific antimalarial therapy given even in the absence of a history of addiction. We do not believe that specific therapy will harm the patient, and it should not interfere with other diagnostic or therapeutic measures if the disease should not be malaria. By this means fatal experiences resulting from failure of diagnosis may be avoided.

In New York City the Health Department has no jurisdiction over the activities of drug addicts having malaria. Since we have successfully infected anopheline mosquitoes with the malaria from the blood of drug addicts who had recovered from the disease, it is obviously desirable to have such control in order to enforce effective treatment as drug addicts must always be considered a potential focus for a malarial epidemic in any community where suitable mosquitoes are abundant. For the same reason it is essential as a public health measure, in a community where suitable anophe-

line mosquitoes and drug addicts are present, to include an effective gametocidal drug in the treatment.

**Summary and Conclusions.** 1. *Falciparum malaria* is endemic in New York City among drug addicts practising the common use of a hypodermic apparatus for the administration of heroin intravenously.

2. The mortality is very high unless effective treatment is given soon after admission to the hospital.

3. In the presence of nervous system or gastro-intestinal involvement chemotherapy should be limited during the acute phase to the administration of quinine dihydrochloride intravenously. When the emergency phase has passed, atabrine should be given orally. To less severely ill patients, or to symptomless carriers of asexual parasites, atabrine alone should be given. Plasmochin should be given as a gametocide to all patients before they are discharged from the hospital. Supportive therapy should include the restoration of fluids, salt, blood, and plasma proteins.

4. A routine for the treatment of the various clinical forms of *falciparum malaria* in the drug addict is outlined.

5. Drug addicts presenting acute obscure syndromes who show signs of having taken heroin intravenously should be treated for malaria until another diagnosis can be established.

6. Heroin addicts having *falciparum malaria* should be under the legal jurisdiction of the Health Department to safeguard the health of the community.

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### $\beta$ METHYLCHOLINE URETHANE.

#### ITS ACTION IN VARIOUS NORMAL AND ABNORMAL CONDITIONS, ESPECIALLY POSTOPERATIVE URINARY RETENTION.\*

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CERTAIN of the derivatives of choline are among the most active drugs known to man and their therapeutic possibilities are just being realized. Those used as medicaments have an action similar

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to the effects which follow stimulation of parasympathetic nerves.<sup>4,15a</sup> Therefore slowing of the heart, peripheral vasodilatation, increased gastro-intestinal activity, increased bladder tone, sweating, salivation and bronchoconstriction are easily demonstrated in animal experiments after giving these drugs.<sup>3</sup> With certain modifications these effects are also found in man and they can be prevented or abolished by atropine.<sup>18</sup> In addition, certain of these drugs have an action like nicotine which is not antagonized by atropine.<sup>4,15a,17c</sup> This action, demonstrated in animal preparations by a rise of blood pressure after atropine, and by certain muscular contractions, is less conspicuous than the parasympathetic effects but, of no known clinical utility, it is certainly undesirable.

Several drugs of the choline series have been used as medications. Acetyl choline, the first discovered, is of great scientific interest,<sup>4</sup> but it has made a poor medicament as it is destroyed in the body with great rapidity. It has a strong nicotine-like action in addition to the characteristic parasympathetic effects.<sup>4,15a</sup>

Acetyl  $\beta$  methyl choline (mecholy) lacks the nicotine-like action and, though not stable, it is far less rapidly destroyed than acetyl choline.<sup>15a</sup> After subcutaneous injection in man intense effects come on rapidly and pass off in a short while.<sup>18</sup> Given by mouth, the action is very mild and the dose required 10 to 30 times the subcutaneous.<sup>18</sup> This drug has been used to arrest paroxysmal tachycardia,<sup>17a,b</sup> in peripheral vascular disease,<sup>10,17a</sup> and for effects on the bladder.

Carbaminoylcholine (doryl) was the first stable choline derivative synthesized. A very active drug of minute dosage, it has a strong nicotine-like action.<sup>6</sup> It has been chiefly used in the treatment of postoperative urinary retention, in peripheral vascular disease, and for its gastro-intestinal action in veterinary medicine.<sup>17c</sup>

Carbaminoyl- $\beta$ -methylcholine, also properly called  $\beta$  methylcholine urethane (B.M.C.U.) was synthesized in 1935, by Major,\* at the suggestion of Simonart,<sup>16b</sup> who from theoretical considerations had anticipated that such a compound would resemble doryl but lack the nicotine-like effect. This expectation proved to be justified for the drug is stable and the nicotine-like effects are very feeble.<sup>16a,b</sup> Its other pharmacologic effects, tested in animal preparations, resemble the parasympathetic-like action of the other active choline derivatives.<sup>5a,b</sup> It is weaker than doryl, the subcutaneous dose for man being about 10 times greater, but also less toxic, the minimal lethal dose for mice, rabbits, and cats, being about 30 times greater than that of doryl.<sup>9,16b</sup> In animal preparations it causes marked intestinal stimulation in doses which have no effect on blood pressure.<sup>17b,20</sup>

Doryl has been used in this clinic since 1934.<sup>17c</sup> During this experience we occasionally encountered uncomfortable side effects not rapidly relieved by atropine, a fact which made us suspect that

\* The drug was supplied through the courtesy of Merck & Co., Inc., Rahway, N. J.



they were due to the nicotine-like effects of the drug. Therefore, we resolved to try B.M.C.U., and this paper is a report of our experiences.

The action of B.M.C.U. has been studied both in healthy volunteers and in patients; over 150 individuals have received it. In postoperative urinary retention the drug has caused prompt emptying of the bladder in many cases. In neurologic conditions its administration has frequently been followed by the replacement of dribbling by automatic emptying of the bladder. We have also employed the drug with benefit in abdominal distention, intestinal atony in children, and peripheral vascular disease.

During this experience we have encountered very few uncomfortable and no dangerous side effects. It is this freedom from untoward action, rather than an increased therapeutic effectiveness, which has made us believe the drug to be superior to doryl.

**Action on Normal Persons.** *Method of Administration.* We have used the chloride of  $\beta$  methylcholine urethane. It is not hygroscopic. Two milligram tablets have been used most frequently, and it was convenient to have 4 mg. and 6 mg. tablets also. Oral administration presented no difficulty. Local irritation after subcutaneous injection was slight. Intravenous injection was not attempted.

*The Action After Subcutaneous Injection.* Twenty-two healthy medical students volunteered to receive the drug and were given subcutaneous doses ranging from 2 to 10 mg. The subjects lay on a couch for a period of at least 15 minutes before the injection and remained there for the duration of the observations. The routine observations were made by Starr or by students working under his direction. All subjects were ignorant both of the type of drug and the dose they were receiving, and some, serving as controls, received injections of water.

The effects of B.M.C.U., summarized in Table 1, came on gradually. If there was any detectable effect on the circulation it appeared in from 5 to 10 minutes. Slight sweating and salivation followed. The gastro-intestinal and bladder effects appeared last, reaching their maximum between 20 and 30 minutes after the injection. After this time all evidence of action gradually diminished but 3 subjects defecated, contrary to their usual habit, between 3 and 5 hours after receiving the drug.

After doses of from 2 to 3 mg., the effects were all very slight, the subject often being at a loss to decide whether he had received an active drug for about 20 minutes. Then the sensation of increased peristalsis and the borborygmi, clearly audible to the listening observers, were perceived.

After doses of from 4 to 6 mg. most subjects were unconscious of any effects on the circulation. The observers noted a flush in less than half the cases and the changes of blood pressure and pulse rate were usually too small to be attributed to the drug. However,

slight salivation was regularly noted and increased sweating of the palms could often be demonstrated. Again increased peristalsis was conspicuous and, in over half the cases, this was accompanied by a definite desire to void so intense that it was called painful in 3 cases.

TABLE 1.—EFFECT OF SUBCUTANEOUS INJECTIONS OF  $\beta$  METHYLCHOLINE URETHANE ON NORMAL YOUNG ADULT MALES.

	Subcutaneous doses.		
	2 to 3 mg.	4 to 6 mg.	7 to 10 mg.
Number of cases receiving the dosage given above . . . . .	5	12	5
Number of subjects who showed effects given below.			
Systolic blood pressure change:			
Less than 5 mm. Hg . . . . .	2	9	2
Fell 5 to 10 mm. Hg . . . . .	3	1	2
Fell over 10 mm. Hg . . . . .	..	..	1
Rose 5 to 10 mm. Hg . . . . .	..	1	..
Rose over 10 mm. Hg . . . . .	..	1	..
Diastolic blood pressure change:			
Less than 5 mm. Hg . . . . .	5	8	2
Fell 5 to 10 mm. Hg . . . . .	..	3	2
Fell over 10 mm. Hg . . . . .	..	..	1
Rose 5 to 10 mm. Hg . . . . .	..	1	..
Pulse rate:			
Change less than 5 . . . . .	4	8	1
Increased 5 to 10 . . . . .	..	1	1
Increase 10 to 15 . . . . .	..	2	2
Decrease 5 to 10 . . . . .	1	1	..
Decrease over 10 . . . . .	..	..	1
Flush . . . . .	3	6	2
Sensation of warmth (early) . . . . .	2	2	2
Sensation of cold (later) . . . . .	..	2	4
Sweating . . . . .	1	6	5
Salivation . . . . .	4	12	5
Lachrymation . . . . .	..	..	1
Increased peristalsis . . . . .	5	10	6
Bowels moved . . . . .	2	1	2
Abdominal cramps . . . . .	..	..	2
Nausea . . . . .	..	..	2
Epigastric discomfort . . . . .	..	1	..
Desire to urinate. . . . .	..	7	2
Pain referred to bladder or urethra . . . . .	..	3	1

Doses of from 7 to 10 mg. were followed by only slight effects on the circulation. The flush was seen in only 2 of the 5 cases receiving this dose. Sweating and salivation occurred in all 5 cases but they were not excessive. Again the gastro-intestinal effects were conspicuous: 2 cases had abdominal cramps, 2 were nauseated, and it was the uncomfortable gastro-intestinal manifestations which caused us to give atropine in 3 instances. The bladder manifestations were prominent in only 2 of the 5 cases; pain referred to the penis was reported by 1 of these.

In subjects with full bladders the desire to void regularly followed the administration of the drug, but if the bladder had recently been emptied, this sensation did not occur.

*Effect on the Cardiac Output.* Seven normal subjects were given the drug while resting on the ballistocardiogram<sup>19</sup> and their cardiac

output was estimated before and after its administration. The results are given in Table 2. In most cases the effects on the circulation were not greater than the changes which occur after injections

TABLE 2.—EFFECT OF SUBCUTANEOUS INJECTIONS OF  $\beta$  METHYLCHOLINE URETHANE ON THE CIRCULATION.

Time.	Subject.	Dose (mg.).	Heart rate (per min.).	Blood pressure (mm. Hg.).	Cardiac output (cc. per min. per lb.).	Remarks.
10.50	G. A.	..	68	110/70	21	Normal.
11.00		3				
11.06			65	110/70	22	
11.20			63	112/68	23	Salivation?
11.33			64	112/80	21	Face feels hot.
11.00	H. E.	..	88	112/94	28	Normal.
11.04		4				
11.20			80	110/78	28	Sweat only in palms; desire to void; peristalsis.
11.32			73	106/87	28	Same.
11.30	J. McC.	..	71	110/75	22	
11.35		4				
11.50			68	110/75	21	Peristaltic sounds increased.
11.55	R. L.	..	70	115/88	25	
12.00		6				
12.13			75	123/85	26	
12.23			72	114/74	28	Slight salivation and sweating.
12.33			78	108/68	26	Peristalsis increased.
11.38	T. G.	..	74	125/90	24	Normal.
11.42		6				
11.50			60	122/90	21	Sinus arrhyth.; peristalsis ++.
12.02			74	122/84	24	Sweating a little; salivating; peristalsis ++; desire to void.
10.30	R. W.	..	65	124/70	20	
10.35		6				
10.40			62	118/66	21	
10.52			60	110/66	22	Peristalsis increased.
11.26	S. P.	..	70	114/80	24	Normal.
11.27		8				
11.34			54	87/60	17	Feels weak; face pale.
11.45			64	104/70	22	Salivating a little; peristalsis +; face not pale.
11.58			64	106/72	22	Same.

of inert solutions, but a significant diminution of cardiac output accompanied marked slowing of the pulse in 2 instances.

*Action After Oral Administration.* Twenty patients received B.M.C.U. by mouth in divided doses which ranged from 2 to 24 mg.

daily. The great majority of these cases did not notice any side effects at all. In no case was any noteworthy effect on the pulse rate or blood pressure detected by the observers. Salivation was never complained of, sweating was noted only occasionally after the larger doses. The development of diarrhea made us reduce the dose on 2 occasions.

Routine hospital blood counts and urinalysis taken during the administration of the drug showed nothing that could be attributed to it. Electrocardiograms taken in 3 persons under its influence were likewise negative.

It is obvious that B.M.C.U., taken by mouth in suitable dosage, produces almost no uncomfortable side effects. While we obtained some evidence suggesting cumulative effects, it was never striking and most patients tolerated a constant daily dose without difficulty.

**Therapeutic Use of the Drug.** *In Postoperative Urinary Retention.* This complication is seen most often in operations on the lower abdomen or on the perineum and it may be looked upon as a reflex depression of the parasympathetic nerves which stimulate the detrusor muscles of the bladder. In its treatment the use of the drug was withheld in all cases until it was evident that catheterization would have to be performed. In a few cases, however, just before the drug was given, the patient voided. This is one of the difficulties encountered in evaluating the functions of any drug in this condition.

B.M.C.U. was administered hypodermically in 2 mg. doses, the patient being previously arranged so that voiding could take place at once if bladder contractions stimulated urination. If voiding did not occur within 20 minutes to half an hour, the same dose was repeated. At times a third dose, and even a fourth, was given at intervals of about 15 to 30 minutes. Untoward reactions were noted in only 1 patient who felt somewhat faint after the administration of the drug. This was relieved by the administration of a hypodermic of 1/150 gr. atropine. In 2 other patients, definite contractions of the bladder with pain were experienced but voiding did not occur. In 1 patient, following a resection of the rectum for carcinoma, it was necessary to catheterize the patient 4 times daily for 11 days after operation. On the 12th day, a supply of B.M.C.U. was obtained. The patient voided after the second dose of the drug and did not require catheterization after that.

The sum of the results is given in Table 3. In all there were 122 attempts to relieve postoperative urinary retention. In this group, voiding followed the use of the drug in 82 cases (68%). In 40 cases, the drug failed to produce urination. In the successful cases, 37 voided after the first dose of the drug, 35 after the second dose, 8 after the third, and 2 after the fourth dose. It is apparent that if the drug is to be effective it will usually act after the first or second dose. After the third dose, there are more failures than successes.

In a few cases retention, once relieved by the drug, recurred and

it was necessary to give B.M.C.U. for several days in order to stimulate urination. There did not seem to be any untoward effects from this repeated use of the drug and when it was effective on one occasion, it was usually effective on subsequent occasions.

TABLE 3.— $\beta$  METHYLCHOLINE URETHANE IN POSTOPERATIVE URINARY RETENTION.  
Given in doses of 2 mg. s.c., usually repeated in 20 to 30 minutes p.r.n.

Type of operation.	No. of success.	No. of failures.
Appendectomies . . . . .	29	8
Herniorrhaphies . . . . .	26	10
Hemorrhoidectomies . . . . .	5	4
Upper abdominal . . . . .	9	6
Colon . . . . .	2	2
Genito-urinary . . . . .	3	1
Others . . . . .	8	9
Totals . . . . .	82	40

*In Other Types of Urinary Retention.* In animal experiments parasympathetic denervation of any organ enhances the action of acetyl choline upon it.<sup>4</sup> Hence one might expect unusually vigorous action of choline derivatives in certain neurologic conditions. However, while we have seen the administration of choline derivatives most successful in cases of urinary retention in neurogenic bladders, the dose required did not differ from that which was successful in other types of disease.

B.M.C.U. has been used in two ways in these cases. First, subcutaneous injections can be used to cause a full bladder to empty; second, given by mouth the drug usually prevents over-distention and results in automatic emptying at a fairly definite content.

For example, a man of 68 years having had a chordotomy to relieve the pain of inoperable rectal carcinoma was entirely unable to void. Six milligrams B.M.C.U. subcutaneously failed, but 10 mg. regularly emptied the bladder about 10 minutes after the injection without any uncomfortable side effects. This dose was given every 6 hours for the following 3 weeks and was successful in every instance. At the end of this time the bladder began to empty automatically and the drug was successfully withdrawn.

In another case, a man of 26 with retention after a laminectomy, 8 mg. subcutaneously caused sweating, salivation, and abdominal cramps but he voided only 50 cc. and 750 cc. was then obtained by catheter. A very similar experience was repeated 4 times during the next 4 weeks when attempts were made to discontinue the continuous drainage. At the end of this time 6 mg. t.i.d. by mouth for 2 days, giving no side effects, was followed by the development of an automatic bladder emptying at about 300 cc.

Experience with two children who suffered from painful over-distention of the bladder without known cause, 3 cases in which the over-distention complicated acute infections, 5 cases of prolonged postoperative retention, and many neurologic cases suggests that,

in the absence of organic obstruction, over-distention can be usually prevented by the administration of choline derivatives given by mouth. For this purpose we now employ 2 mg. B.M.C.U. t.i.d. and if, after 2 days' trial, this is unsuccessful we increase the dose until either the desired effect is achieved or uncomfortable side effects become prominent. If uncomfortable symptoms appear, atropine will relieve the patient very rapidly.

We have made no study of the effects of B.M.C.U. in post-partum retention of urine, but we have frequently supplied the drug to friends in contact with such cases and know of many instances in which it was used successfully.

*Gastro-intestinal Effects.* We have used B.M.C.U. 10 times in cases of abdominal distention and occasionally it has been extremely successful. We can cite such an experience in a case markedly distended for 1 week during the passage of a renal calculus. During the preceding 3 days he had received at appropriate intervals a rectal tube repeatedly, 3 flaxseed poultices, castor oil, 2 milk and molasses enemas, 5 ampules of pitressin, and 1000 cc. of 5% glucose in physiologic saline solution, without relief. Then, with a rectal tube in place, the administration of 4 mg. of B.M.C.U. subcutaneously was followed by markedly increased peristaltic sounds, abdominal cramps, and the expulsion of large amounts of flatus 12 minutes later. Twenty-five minutes after the drug the abdomen was soft for the first time in a week.

Unfortunately, dramatic results of this type were secured in only 2 of 10 trials. The drug regularly increased the peristaltic sounds in such cases and usually caused cramps, but the expulsion of flatus did not follow in 5 of the 10 instances in which the drug was used alone. However, the insertion of a rectal tube or the giving of an enema during the drug's action produced the desired result on 3 occasions.

In summary, we have seen B.M.C.U. fail where pitressin, given later, succeeded, and we have seen it succeed after many other measures had failed. Sometimes extremely successful, in other instances its effect is disappointing, and we believe that a similar uncertainty exists for all the remedies regularly used in the treatment of distention. The advantage of this drug over most of the others employed in this condition is that any untoward effects could be entirely overcome by its antidote atropine.

In 2 cases, remarkably similar, the laxative action of the drug was successfully employed.

CASE 1.—L. D., a colored boy of 12, a patient on Dr. Gitting's service, had been well till the age of 6. Since that time he has had 6 admissions to the hospital because of extreme constipation. He often went a week without defecation and the abdomen was usually full of fecal masses. The child was subnormal mentally and had a B. M. R. at times subnormal, —20% on 2 occasions, within normal limits on 2 more occasions. Roentgen ray disclosed a greatly dilated sigmoid. A large number of laxatives and

enemas, alone and in combination, had failed to produce a regular habit and thyroid had been given unsuccessfully on various occasions. B.M.C.U. was given in doses of 2 mg. t.i.d., later 4 mg. t.i.d. by mouth, and on this régime he had a normal bowel movement daily until his discharge 6 days later. Sent home on the drug he was seen 1 month later and seemed to the attending physician to be doing better than he had for years.

CASE 2.—R. R., a boy of 12, was studied by Dr. G. H. Kagen at St. Christopher's Hospital. He had been constipated since birth having had no bowel movement without enemas or laxatives. The child was mentally retarded. Abdominal fecal masses could be palpated. Given B.M.C.U. in ascending doses beginning at 2 mg. t.i.d., his bowels soon began to move regularly. Whenever they failed to move the dose was raised, the highest attained being 2 mg. 6 times a day. Under this régime he had a daily stool for 3 weeks. Then, on December 30, 1939, the drug was omitted and his bowel action became most irregular, the child often going 4 days without a stool which was then usually secured by enema. On January 16, 1940, the drug was resumed in doses of 10 mg. daily. Movements were infrequent until January 24 when the first adequate evacuation occurred. Thereafter he had a good movement every 2nd or 3rd day until February 8th when the drug was omitted without the patient's knowledge, an inert tablet being substituted. He had no stool during the following week.

*Paroxysmal Tachycardia.* The slight action of B.M.C.U. on the circulation gave us reason to expect that it would be far inferior to mecholyl in arresting attacks of paroxysmal tachycardia and we have not used it for this purpose. Nevertheless, it seemed possible that it might prevent such attacks and for this purpose its long continued action would make it superior to mecholyl.

The ordinary case of paroxysmal tachycardia has attacks so infrequently and at such irregular intervals that the effectiveness of a drug designed to prevent them is very difficult to judge. At length we found a case having attacks so frequently that a study became possible.

CASE 3.—A. F., an intelligent white man of 53, kept a careful record of his attacks in a notebook. Beginning in childhood, for the past few months he had had attacks once or twice a day. Many of these he could arrest himself by bending forward, the others usually stopped spontaneously within 2 to 4 hours. Ekg. showed typical auricular tachycardia. Otherwise his health was excellent.

After 5 days in the hospital as control period, the patient was given B.M.C.U. in ascending doses from 4 mg. to 8 mg. t.i.d. by mouth, receiving the largest dosage, 24 mg. daily, for a week. He noticed no side effects of the drug but the number of his attacks was unchanged. The patient believed that he was better able to arrest the attacks while he was taking the drug, but we had seen him stop several with great ease when not under its influence and so we were left in doubt whether the effect was a real one. Quinidine sulfate in doses of 0.2 gm. b.i.d. likewise had no influence in preventing attacks in this case.

Therefore we have obtained no evidence that choline derivatives are of value in preventing attacks of paroxysmal tachycardia although the action of mecholyl in arresting such attacks is well established.<sup>17a,b</sup>

*Peripheral Vascular Disease.* We have encountered 1 case of Buerger's disease in which severe rest pain was completely relieved by injections of either 0.4 mg. doryl or 4.0 mg. B.M.C.U. The patient was unable to distinguish between the two drugs but injections of inert solutions were identified immediately.

Spectacular relief of this type of pain by choline derivatives has occurred only rarely in our experience,<sup>17a,c</sup> but in a few patients this action has been very striking, the relief exceeding that secured by opiates. Slighter degrees of relief have occurred more frequently but in a majority of cases little, if any, relief can be secured by vasodilator drugs. Doryl and B.M.C.U. were identical in their effects on peripheral vascular disease in our experience.

A very interesting result, perhaps an effect on cerebral vessels, was secured in a case who also had peripheral vascular disease.

CASE 4. A man of 65, with a long story of bouts of manic-depressive psychosis, had had a transient left hemiplegia 6 years before and intermittent claudication of the right thigh for 2½ years. Recently he had been subject to attacks of pallor and cold in the right leg. No pulses were palpable in either leg and there was atrophy of the right calf muscles. There was marked sclerosis of all palpable arteries and a positive Babinski on the left, but the physical examination was otherwise negative and the routine laboratory tests were normal. B. P. 125/80.

The day before admission he had been seized by attacks of transient numbness and weakness involving the left arm and left side of his face, with drooling from the left corner of his mouth. During these attacks the reflexes were normal, the parts involved flaccid. The attacks lasted about ½ hour and between them recovery was complete.

The patient had had 14 of these attacks in the 24 hours preceding admission. Under the belief that they were due to spasms of cerebral vessels analogous to those occasionally seen in his right leg, he was given 6 mg. B.M.C.U. subcutaneously and then 4 mg. t.i.d. by mouth. After the first dose the attacks stopped abruptly, he had only 3 mild ones, numbness without weakness, during the next 7 days and no serious attacks after that. He underwent slow mental deterioration and died, apparently of manical exhaustion about 3 months later.

*Hypertension.* Six out-patients suffering from essential hypertension of many years' duration were given B.M.C.U. by mouth, under the direction of Drs. H. A. Schroeder and Wm. A. Jeffers. Increasing amounts, ranging from 2 to 6, 10, and 12 mg. daily were given in divided doses over periods the shortest of which was 3 weeks, the longest 10 weeks. Placebo tablets of the same size and shape were given in control periods. The average blood pressure of these cases showed no significant change when they were taking the drug.

One patient had a diarrhea when taking 12 mg. daily but tolerated 10 mg. easily. There were no other untoward effects and this is the chief interest in the series.

*Untoward Effects and Their Relief by Atropine.* Our clinical results are what might be expected from the pharmacology of this drug. Our experience with untoward effects can be illustrated by



the experiments on normal volunteers in which the dose was deliberately raised to provoke them.

CASE 5. A medical student, A. W., age 23, weight 136, had been occasionally subject to asthmatic attacks. Given 10 mg. B.M.C.U. subcutaneously, the characteristic action began in about 3 min.; 5 min. after the drug he was slightly nauseated and 5 min. later he had abdominal cramps. Fifteen minutes after the drug he had a mild asthmatic attack. Atropine sulphate (0.6 mg. (gr.  $\frac{1}{100}$ )) was given subcutaneously and the site of the injection massaged vigorously. The asthma was relieved within 3 minutes but mild sweating, salivation, and cramps persisted and muscular tremors, accompanying a sensation of cold, appeared. The atropine was repeated 15 min. after the first dose and relief was complete within 10 minutes. Changes of blood pressure and pulse rate were negligible during this experience, except that after atropine the pulse rate diminished, as is regularly the case when that drug is used alone in small doses.

CASE 6. Another normal subject, H. P., age 23, weight 152 lbs., was given 8 mg. B.M.C.U. subcutaneously. The usual action appeared gradually but 30 min. after the administration of the drug abdominal cramps and pain in the bladder made him extremely uncomfortable. Atropine (0.6 mg. (gr.  $\frac{1}{100}$ )) was given subcutaneously and the discomfort disappeared in 15 min. However, about 3 hours later abdominal cramps and perspiration returned. A second dose of atropine then brought complete relief. Again there was no noteworthy effect on the circulation at any time.

Our experience with the untoward effects of B.M.C.U. may be summarized as follows. Like the other active choline derivatives used as medicaments, the drug produces asthma in patients subject to this disease. In other subjects, if the dose is raised until uncomfortable symptoms appear, abdominal cramps and painful spasms of the urinary tract appear first, at a time when changes in the circulation are usually negligible, and sweating and salivation only slight.

Subcutaneous doses of 10 mg. usually produced acute discomfort in medical students but many older patients could take this dose without any discomfort at all. Age seems to be a factor in the dosage of B.M.C.U. as it is with mecholyl.

Untoward effects can be relieved by atropine but a dose of 0.6 mg. (gr.  $\frac{1}{100}$ ) given subcutaneously often proves too small. We now use 1.2 mg. (gr.  $\frac{1}{50}$ ) subcutaneously and massage the site of the injection. Relief follows in a few minutes. Occasionally the choline action, outlasting that of the atropine, has reappeared several hours later, requiring additional atropine.

**Discussion.** A promising field of usefulness of B.M.C.U. is in combating the retention of urine not caused by organic obstruction. By its use catheterization after operation has been reduced to  $\frac{1}{3}$  of its former frequency, to the relief of both the patients and the staff. A very similar result can be secured by doryl and the literature on this point is summarized in Table 4. When our data are compared it will be seen that we were less successful than some, more successful than others who used doryl. The grand average is slightly in favor of doryl, but in our own rather brief experience the use of

doryl in postoperative retention was not quite as successful as the published data had led us to expect, so we do not believe that there is a significant difference between the effectiveness of the two drugs.

We regard B.M.C.U. as superior to doryl because of the lack of side effects. Only rarely have our patients experienced anything uncomfortable. It is true that the side effects after doryl are usually of minor importance, but sweating, nausea, faintness, and malaise, were fairly common after that drug, both in our experience and in that summarized in Table 4. Also, especially after oral administration, doryl was irregular in its action and uncomfortable symptoms, chiefly malaise and nausea, appeared in some persons after receiving less than  $\frac{1}{2}$  the dose easily tolerated by others.<sup>17c</sup> The action of B.M.C.U. has been much more reliable in our experience. In addition, certain untoward effects of doryl could not be relieved by atropine,<sup>17b</sup> while uncomfortable symptoms after B.M.C.U. have yielded readily to atropine.

TABLE 4.—DORYL IN URINARY RETENTION, POSTOPERATIVE AND POSTPARTUM.

Author.	Type of case.	Subcutaneous dose, mg.	Success.	Partial success	Failure.
Schulze <sup>13</sup>	Postop.	0.25	80	..	28
	Postpart.	repeated if necessary	133	..	15
Moir <sup>8</sup>	Postop.	0.25	10	4	4
	Postpart.	0.25	4	4	12
Maxwell <sup>7</sup>	Postop.	0.25	15	..	2
		repeated twice if necessary			
Nolting and Althebe <sup>11</sup>	Postop.	0.25	19	..	5
	Postpart.	0.25	39	..	4
Officer and Stewart <sup>12</sup>	Postop.	0.25	38	5	12
Brimberg <sup>1</sup>	Postop.	0.25	16	2	2
		repeated if necessary			
Schwartz <sup>14</sup>	Postop.	0.25	8	..	12
Kreutzman <sup>7</sup>	Postpart.	0.25	25	..	2
	Postop.	repeated once if necessary	25	..	3
Brown <sup>2</sup>	Postop.	0.25	25	..	5
Totals	Postop.	..	236 (74%)	11	73
	Postpart.	..	201 (85%)	4	33

Therefore, although the difference between the action of doryl and B.M.C.U., when given in clinically equivalent doses, is usually not striking, a prolonged experience indicates that the theoretical advantage of B.M.C.U. over doryl, its lack of nicotine-like action, is a practical advantage as well.

The knowledge that atropine completely obliterates all the effects of B.M.C.U. has given us confidence to explore the higher ranges of dosage as we would not have dared to do with doryl. Recent experience indicates that some patients tolerate large doses

extremely well, had we known this earlier our percentage of success would have been higher.

In the treatment of distention B.M.C.U. is often successful but we make no claim that it is more successful than other well known procedures. Its advantage lies in the fact that its action, if untoward, can be abolished at will. B.M.C.U. has also been used successfully in 2 cases of extreme constipation in children.

In peripheral vascular disease the effects of B.M.C.U. seem much like those of doryl; in an occasional case it causes striking relief of rest pain but the patients thus relieved are only a small fraction of the total number of these cases.<sup>17c</sup>

We have no evidence that the drug is of value in either hypertension or paroxysmal tachycardia.

In recent weeks our technique for the treatment of functional urinary retention has been as follows. As soon as the diagnosis is made we start B.M.C.U. giving 2 mg. t.i.d. by mouth and this is continued until voluntary or automatic voiding begins and then slowly withdrawn. In addition, if the bladder becomes over-distended we provide a bedpan and then give 2 mg. B.M.C.U. subcutaneously. If there is no voiding in half an hour we repeat this dose. If still unsuccessful within the next half hour, especially if pain is produced without voiding, we usually catheterize. But if the bladder becomes over-distended again we give 4 mg. subcutaneously repeating the dose in one-half hour if necessary before catheterizing. If there are no disagreeable side effects we continue to raise the dose in this manner until success is attained; in 1 case 10 mg. was required.

Any dose which empties the bladder once may be expected to have the same effect if retention occurs again. Therefore the successful dose is used until voluntary or automatic emptying is established.

The provision of a pan before administering the drug is an important detail of the technique, since the desire to void comes on quite rapidly in some persons; it can be resisted, and it may pass off if preparations are delayed.

**Summary.** 1. Beta methylcholine urethane, a stable choline derivative synthesized by Major at the suggestion of Simonart, has been studied in the clinic.

2. Having the typical choline action, this drug produces effects analogous to stimulation of parasympathetic nerves. These effects can be abolished by atropine. It is more stable than mecholyl and largely lacks the undesired nicotine-like action of doryl. It is probably for this reason that uncomfortable side effects are at a minimum. We regard it as superior to doryl for use in the clinic.

3. Given to 25 normal young adults, in suitable dosage, the drug caused increased peristalsis and a desire to void when its action on the heart and circulation, on salivation, and on sweating, was minimal.

4. The drug caused emptying of the bladder in 68% of 122 patients with postoperative urinary retention, reducing the necessity for catheterization by two-thirds.

5. It has also been used with benefit in patients with neurogenic bladders and in certain cases of abdominal distention, extreme constipation, and peripheral vascular disease.

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### ALLERGIC INTESTINAL BLEEDING IN THE NEWBORN; A CLINICAL SYNDROME.

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WHILE the occurrence of intestinal hemorrhage in children with gastro-intestinal disturbances due to allergy has long been recognized, this important manifestation of allergy in the newborn period seems to have escaped description in the pediatric literature. In the past 3 years, 6 such patients have been seen. The histories of these cases, which differ from each other only in very minor details, are so dramatically identical, as to form a definite clinical syndrome.

The following cases are typical:

CASE 1.—G. G., with a family history of allergy, was of normal birth, and weighed  $9\frac{1}{2}$  pounds at 1 month of age. Evaporated cow's milk feeding was begun at birth. For the first 3 weeks of life there was considerable "colic," during which period the nurse in charge was constantly demanding an increase of food, for the child seemed always hungry. Vomiting did not occur. At the age of 3 weeks, the stools, which until then had been normal, increased in frequency, became soft, and contained considerable flecking of bright red blood. The amount of blood in the stools increased until the entire stool mass, normal in form, was peppered throughout with millet-

seed sized specks of blood, and contained much mucus. The "colic" was exaggerated. Fever was not present.

After eliminating other possible causes of abnormal bleeding (melena), the diagnosis of allergic bleeding was considered. The child was then taken off cow's milk and put on human breast milk feedings. Within 48 hours after changing the feeding, the bleeding from the bowel ceased and the "colic" disappeared. The baby now seemed satisfied and the excessive hunger was no longer present.

One week later the feeding was again changed to cow's milk and there was a prompt return of the bloody stools within 24 hours. The cow's milk was then discontinued and breast milk started again, with prompt clearing of the blood from the stools a second time. After 3 months of breast milk feeding, goat's milk was substituted and was well tolerated. Solid foods were added to the diet at the usual time. At 1 year of age this child developed another allergic manifestation, typical diathetic eczema.

*Summary.* This baby, born of an allergic family, gained weight well and seemed in good health despite the early development of intestinal "colic." This latter symptom and excessive hunger were the only complaints until melena appeared. There was a prompt disappearance of symptoms on change from cow's to human breast milk. Goat's milk was later well tolerated. The child subsequently developed eczema.

CASE 2.—R. C., with a strong maternal family history of allergy, was born normally at term, weighing 7 pounds. He was immediately placed on feedings of evaporated cow's milk, on which he gained rapidly during the first 4 weeks of life. However, he seemed always hungry. "Colic," which developed at about 1 month of age, was partially relieved with sedatives. Even though large gastric peristaltic waves (indicative of pylorospasm) were visible on examination, vomiting did not occur. About 3 days after the onset of "colic," the stools became more frequent in number (5 to 6 daily) contained mucus, and were flecked throughout with small pinhead-sized blood specks. The blood was bright red. On 2 or 3 occasions the blood was free of fecal matter (about 1 or 2 drams in quantity). Fever was not present.

Within 48 hours after changing the feedings from cow's to goat's milk all of the intestinal symptoms disappeared and the stools became normal in character. At 5 months of age this child developed severe diathetic eczema.

*Summary.* This baby did well for the first 4 weeks on cow's milk feedings. He then developed pylorospasm with "colic." (It is interesting that vomiting did not occur even though large gastric peristaltic waves were present.) Prompt relief of symptoms resulted within 24 hours after removing cow's milk from the diet. This boy subsequently developed diathetic eczema.

CASE 3.—M. S. R., with a strong bilateral family history of allergy, was born normally at term. The birth weight was 5 pounds, 10 ounces. The weight at 5 weeks was 8 pounds, five ounces. Evaporated cow's milk feedings were begun at birth. Because of a tendency to loose and mucus-containing stools, many changes in the formula were tried, cow's milk always being used. The "colic," which did not appear until the third week of life, became suddenly worse 2 days prior to his hospital admission at the age of 5 weeks. On the first of these latter 2 days, the baby passed 6 bloody stools.

During the next 24 hours the amount of blood passed on several occasions was sufficient to wet a large part of each diaper. Bright red in color, the blood was passed with the stools, but seemed not admixed with them. An enema given on admission to the hospital returned bloody. (The cells on microscopic examination appeared fresh.) Due to the blood loss, a moderately severe anemia had developed. Because of the severe intestinal hemorrhage, the diagnosis of bleeding from a Meckel's diverticulum had been previously made and surgical intervention considered. Vomiting did not occur and fever was not present.

After clinical and laboratory studies, other causes for melena could be eliminated. Since bleeding from a Meckel's diverticulum is very rare at this early age, and because this case so closely resembled the others with milk allergy, the baby was taken off cow's milk and put on human breast milk feedings as a trial. Within 24 hours after this change in feeding, no fresh blood was found in the stools. After 48 hours the blood had completely disappeared, the stools were normal, and the "colic" had ceased, not to return again. Five days later the formula was changed to goat's milk. The baby has now been on goat's milk for 12 months without any return of the original symptoms.

*Summary.* This baby gained weight and seemed in good physical condition despite the early development of "colic" and of loose stools containing mucus. The bleeding from the bowel was so great as to produce anemia and suggest bleeding from a Meckel's diverticulum. (Two gastro-intestinal Roentgen ray studies were negative.) There was a prompt disappearance of all symptoms upon removing cow's milk from the diet.

CASE 4.—F. W. S., with a strong bilateral family history of allergy, was born by Caesarean section weighing 7 pounds, 7 ounces. Evaporated cow's milk feedings were begun at birth. This baby gained weight normally and seemed well until 5 weeks of age. At this time frequent vomiting and the passage of 5 to 6 loose, bloody stools daily began and continued until admission to the hospital at 7 weeks of age. The child had considerable "colic" and expelled much flatus. The blood in the stools was bright red and well mixed with the fecal matter. The stools contained considerable mucus.

From a period soon after birth this baby had peculiar "choking" attacks during which he became cyanotic and occasionally seemed in shock. These attacks over a period of subsequent months, have become less frequent and now appear as typical asthmatic attacks.

On examination at the age of 7 weeks, the baby was found to have a moderately severe anemia. Large gastric peristaltic waves were visible (pylorospasm). Roentgenograms of the lungs showed what may have been aspiration (lipoid) pneumonia. (We have seen similar lung changes in patients with pyloric stenosis.) On one occasion the mucus from the stool contained many eosinophils. Fever was not present.

After excluding other causes of melena, a diagnosis of allergic bleeding was made, and the formula changed from cow's milk to evaporated goat's milk. Within 48 hours of this change, the blood and mucus disappeared from the stools, and the vomiting and "colic" ceased. Following this, the gastric peristaltic waves were no longer observed.

After about 3 weeks on the goat's milk the intestinal symptoms reappeared, the stools becoming frequent and containing blood and mucus. With elimination of milk from the diet and the change of the formula to a soy-bean mixture, the intestinal symptoms permanently disappeared.

This child at the age of 4 months developed diathetic eczema.

*Summary.* This baby had peculiar "choking" spells which developed soon after birth, and now has what appears to be typical asthma. Beginning at the age of 5 weeks, this child developed frequent, loose, bloody stools containing mucus, with evidence of pylorospasm and "colic." The intestinal symptoms disappeared on removing cow's milk from the diet and changing the feedings to goat's milk. This baby proved later to be sensitive also to goat's milk, as the symptoms returned after 3 weeks on this food, to disappear permanently when a soy-bean feeding was substituted. Eczema has subsequently developed in this patient.

The summaries of each of these cases show a striking similarity. There was in each instance a strong family history of allergy, usually bilateral. In all of them cow's milk feeding was started immediately or within a few days after birth. Hunger, or what was thought by the mother to be hunger, was a constant complaint. In retrospect, this "hunger" probably represented abdominal discomfort, which was manifested as "colic." However, despite this abdominal distress, weight gain was not impeded; in fact, it was above average. The "colic" first appeared about 3 weeks after the onset of cow's milk feeding, and became progressively worse. Within a few days after the onset of the abdominal symptoms, loose stools appeared, soon to contain mucus and bright red blood. The amounts of blood varied from small pinhead-sized clots well admixed with the slimy stool, to profuse hemorrhage containing no fecal matter whatsoever. In each case there was prompt and complete disappearance of the blood from the stools within 48 hours after the withdrawal of cow's milk from the diet. The mucus in the stools and the "colic" disappeared shortly afterwards.

It is interesting that in 2 of the children, the "colicky" pains were associated with visible, large, gastric peristaltic waves, indicative of pylorospasm. This was probably a part of the generalized gastrointestinal spasm which disappeared when the other symptoms were relieved.

All the infants except one have developed diathetic eczema within a few months after the onset of the intestinal symptoms. One child developed asthma.

In none of the cases was bleeding from any other part of the body observed. In each case the bleeding and clotting times were normal. In no case did bleeding from the intestinal tract recur after the cows' milk was withdrawn, except in Case 4, where the baby seemed also sensitive to goat's milk, and where the melena disappeared when goat's milk was withdrawn and the child placed on a soy-bean mixture.

Intracutaneous tests with milk protein performed on the infants were negative. Passive transfer tests were not performed; it would seem useless to make them for cow's milk sensitization in these very young babies, for Lippard<sup>1</sup> found in a group of 28 eczematous infants,

given cow's milk over a period averaging 5 months, that only 1 of these babies had a positive passive transfer test for milk, even though 22 of them had developed antibodies against cow's milk (demonstrated by a positive complement fixation test for this milk).

Fever was not an accompanying symptom.

**Discussion.** These cases of gastro-intestinal allergy were all identical in that they were each cow's milk sensitive, having an onset of intestinal hemorrhage about 3 to 5 weeks after the starting of the cow's milk feeding, and a disappearance of the melena within 48 hours after the withdrawal of the cow's milk from the diet. In all except 1 case, goat's milk was well tolerated.

This interval of 3 to 5 weeks between the taking of cow's milk and the onset of severe gastro-intestinal symptoms, chiefly melena, is explainable by the observation of Lippard, Schloss, and Johnson,<sup>2</sup> who demonstrated that such a period of time was necessary for the maximal development of anti-cow's milk antibodies by the infant ingesting cow's milk. In other words, gastro-intestinal symptoms come on when the child is sufficiently sensitized (actively) to the cow's milk.

From the very rapid disappearance of symptoms, in every instance within 48 hours after the removal of cow's milk, one might assume that the intestinal spasm and hemorrhage were a local (intestinal wall) reaction. The mechanism of the local reaction is probably explainable by the following theory: First, the intestinal tissues are actively sensitized by the earlier ingestion of cow's milk or possibly through intra-uterine sensitization; and second, the severe intestinal reaction occurring subsequently, results from the presence of antigen (cow's milk) locally in the intestinal lumen, acting on the previously sensitized tissue. (This local reaction is similar to that seen in the positive skin test reactions or in contact dermatitis.) If this theoretical consideration were not valid and if the local effect were not the true mechanism, it would be difficult to explain the prompt disappearance of symptoms on withdrawal of the cow's milk from the diet. Lippard, Schloss, and Johnson<sup>2</sup> and Lippard<sup>1</sup> have shown that antibodies remain in the circulation of allergic (eczematous) babies for some time (months); in addition, the antigen (cow's milk) which is absorbed and present in the blood could hardly disappear so rapidly with the cessation of cow's milk feedings. Thus, if the intestinal phenomena were simply a local manifestation (shock organ) of a generalized reaction, the improvement after cow's milk withdrawal should be slow.

Since most of the babies could tolerate and remained well on the goat's milk feeding, it seems likely that sensitization in these cases was due chiefly to the lactalbumin fraction. If human breast milk is available, it is, of course, the preferable substitute, for the child may be also sensitive to goat's milk, as was found in one of the above cases.



It is not surprising that these infants, exhibiting such violent allergic manifestations in the newborn period, would develop other evidences of allergy at an early age (eczema). For this reason great care should be exercised when new foods are added to the infant's diet. A sufficient time interval between each new food addition should be allowed to observe whether or not allergic symptoms will develop.

It cannot be too strongly emphasized that even though there is considerable evidence to suggest an allergic etiology for the melena of a small infant, all of the more serious causes for intestinal hemorrhage should be thoroughly excluded before a final diagnosis of allergic melena is made. However, while this differential diagnosis is being investigated, one might safely remove the cow's milk temporarily from the diet and place the child on goat's milk feedings.

Even though the cases presented here are clearly cow's milk sensitive, there is no reason to believe that other foods given during this age period might not produce a similar clinical picture.

**Summary.** A well-defined clinical syndrome, in which the occurrence of intestinal bleeding is a prominent feature, is described in infants between 3 and 5 weeks of age who have developed an allergic sensitivity to cow's milk. "Colic" is also a constant symptom. These intestinal disturbances disappeared within 48 hours after the removal of cow's milk from the diet. In all except 1 case goat's milk was well tolerated.

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### THE INCIDENCE OF ASPIRIN HYPERSENSITIVITY.

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IN 1937 Prickman and Buchstein<sup>7</sup> stated that aspirin hypersensitivity is the most common form of drug allergy, and that it is to be looked for in individuals with a family history of allergy, and especially in asthmatics with nasal polyps. They reviewed the literature,\* summarized a series of 33 cases of hypersensitivity to aspirin found there, collected 62 cases of their own and emphasized the dramatic consequences that may follow the ingestion of the drug by sensitive individuals. Four fatal cases have been reported.<sup>4-6,9</sup>

\* For complete bibliography to 1937, see Prickman and Buchstein's article.

They were all asthmatic individuals. Three had given a previous history of severe reactions to aspirin. In 2 cases nasal polyps had been demonstrated. It is generally conceded that aspirin in certain instances may be a very dangerous ingested, but proof seems to be lacking that aspirin hypersensitivity is as common as might be inferred from such reports. It is the purpose of the present study to assemble additional evidence concerning the incidence of aspirin hypersensitivity and to evaluate further its danger to allergic individuals.

The histories of 467 private and clinic patients were reviewed to determine if possible the incidence of aspirin sensitization among them. More than half of our patients were asthmatics. All of them were regarded as having some sort of allergy. Each was asked when his history was obtained: "Do you take aspirin?" and "What effect have you noticed from it?" The answers were recorded on the history sheet of each patient.

In 5 of these 467 cases aspirin or salicylates may have influenced the development of allergic symptoms. A patient with angioneurotic edema involving the lips, cheeks, and eyelids thought the taking of Stanback\* precipitated her attacks. Another patient thought Stanback might cause her to develop an attack of asthma. A patient with angioneurotic edema thought her attacks were induced by aspirin or by B. C. Powders.\* A patient with asthma complained of nausea after taking aspirin. Another reported that wheezing sometimes followed the use of salicylates. In no instance have we encountered the dramatic consequences occasionally described in the literature.

As has been pointed out by Cooke<sup>2</sup> differentiation must be made between drug idiosyncrasy and drug allergy. Drug idiosyncrasy is simply a normal pharmacologic response carried to an unusual degree. Drug allergy is an entirely different phenomenon which is sometimes produced by unbelievably minute quantities of the offending chemical.

Many persons complain of gastric discomfort, some of tachycardia, and others of mental exhilaration after taking aspirin. Nausea, vomiting, diarrhea, ringing in the ears and mental excitement are also recognized as early signs of aspirin overdosage, and in the susceptible even small doses may produce disagreeable symptoms. These disagreeable symptoms are irritative and toxic effects and not manifestations of allergy.

A group of 50 allergic patients were selected for detailed questioning. It was sought to determine whether they had experienced any of the above symptoms after taking aspirin and what had been their experience in taking quinine. Of the 50 persons questioned in detail, 44 suffered from asthma; 3 had atopic dermatitis; 1, urticaria; 1, vasomotor rhinitis; and 1, hay fever. All but 3 admitted taking

\* Contains aspirin, acetanilide, potassium bromide and caffeine.

aspirin, or a compound containing it; some took it as frequently as two or three times a week; some took it only once a year. Only 4 had experienced unpleasant symptoms which they thought referable to it. Two had rapid pulse and flushing, 1 had a depressed feeling and 1 complained of wakefulness. Of its effects on the allergic disorder itself, 33 stated they had never taken it for this purpose, 5 that it had had no effect, while 12 thought it had been beneficial. In none were allergic symptoms provoked. We found that 17 had never knowingly taken quinine. Those who had used it had done so only occasionally. Skin rashes had followed its use in 2 cases and in 1 instance dizziness resulted. No allergic symptoms were provoked.

To throw further light on the question of the frequency of the aspirin hypersensitivity in allergic patients, we undertook to give 5 grains of aspirin by mouth to each of 103 consecutive admissions to the Immunology Clinic, after a negative history of such sensitivity was secured. Each patient was observed at the end of 10, 30, 60 and 120 minutes, and note was made as to whether or not the allergic symptoms of which he initially complained were aggravated or improved. In this group there were fourteen who maintained that "the medicine" had made them feel better. Two asthmatics stated that they had a slight sense of constriction in the chest. In both instances the symptoms were transitory and may not have been the result of the drug. None of these 103 patients reacted violently to aspirin.

Patch tests with aspirin in our experience have been uniformly negative. We have not attempted scratch or intracutaneous tests in this type of sensitivity.

We have many times encountered non-allergic patients who said they could not take aspirin, but who could usually be given it without any discomfiture if it were disguised in a capsule.

The opinion of a group of 95 allergists of this country concerning the frequency of aspirin and quinine sensitivity was sought. We had 46 answers to the questions: "How many cases of aspirin sensitivity have you encountered and what percent does this represent of all the allergic patients you have seen?" and "How many cases of quinine sensitivity have you encountered and what percent does this represent of all the allergic patients you have seen?" A number of correspondents gave figures that were admittedly approximations, but when everything is considered this did not negative the value of the experience of so large a group. Omitting those answers which were too indefinite to use, and one or two estimates which were out of line with the average experience of the group, we calculated that the total number of allergic patients seen by the 22 physicians whose answers could be used, was approximately 90,000. Among this large number of patients, approximately 170 had shown evidence of aspirin sensitivity. This represents 2 in 1000 (0.2%).

Among the same group of patients 71 instances of quinine sensitivity were reported.\*

ASPIRIN AND QUININE SENSITIVITY. OPINION OF FORTY-SIX ALLERGISTS  
TABULATED.

Location.	Number seen.		Per cent.		Total patients.	Remarks.
	A.	Q.	A.	Q.		
1. Alabama . . .	1	3	0.2	0.6	500	
2. Louisiana . . .	2	1	0.25	0.12	800	
3. New York . . .	12±	1±	0.1	0.01	10,000	
4. Illinois . . .	10±	10±	0.2	0.2	5,000	
5. Colorado . . .	0	3	0	0.03	10,000	
6. Michigan . . .	4±	2±	0.1	0.05	4,000(?)	
7. Ohio . . .	3	2	0.6	0.4	500	
8. Virginia . . .	9	0	3.6	..	250	
9. Missouri . . .	5	3	0.1	0.05	5,000	
10. Louisiana . . .	5	0	0.5	..	1,000	
11. Missouri . . .	10	5	0.5	0.25	2,000	
12. Ohio . . .	14	2	0.1	0.01	14,000	
13. Illinois . . .	4	6	1.0	1.5	400	
14. Ohio . . .	20	7	0.4	0.15	5,000	
15. New Jersey . . .	15	5	0.5	0.15	3,000	
16. New York . . .	2	2	0.4	0.4	500	
17. Virginia . . .	2	6	0.5	1.5	400	
18. Washington . . .	4-5	2-3	1.0	0.5	500	
19. Pennsylvania . . .	1	0	0.1	0	1,000	
20. Pennsylvania . . .	15	3	0.1	0.02	15,000	
21. Virginia . . .	120±	120±	2.0	2.0	6,000	
22. Michigan . . .	4	5	0.2	0.25	2,000	
23. Wisconsin . . .	27	0	0.5	0	5,400	
24. Minnesota . . .	117	6				
25. Nebraska . . .	5	2				
26. Texas . . .	10±	15-20	..	..	..	Very small per cent
27. New York . . .	2	1+				
28. Pennsylvania . . .	6	1				
29. Illinois . . .	3	0				
30. Alabama . . .	2	1	1.0(-)	1.0(-)		
31. New York . . .	1	1	..	..	..	In several thousand cases
32. California . . .	15	Few	..	..	..	Very small per cent
33. Arizona . . .	25±	?	..	..	..	Fraction of 1 per cent
34. New York . . .	6-12	3	1.0(-)	1.0(-)	..	
35. Alabama . . .	Few	Numerous	..	..	..	Aspirin rare, quinine frequent
36. Texas . . .	Few	Few				
37. Massachusetts . . .	..	..	0.25±			
38. Tennessee . . .	..	..				
39. Georgia . . .	..	..	5.0	1.0	..	5 times as many aspirin as quinine
40. Minnesota . . .	0	0				
41. New York . . .	Common	Common				
42. Pennsylvania . . .	?	?				
43. Missouri . . .	Few	Few			..	Very small per cent
44. Arizona . . .	Many	Rare	25.0	?		
45. Illinois . . .	Many	1				
46. Minnesota . . .	117*	6				

A., Aspirin. Q., Quinine.

\* From same clinic as 24.

We next undertook to discover the annual consumption of aspirin and quinine in this country. We found that in 1937 there was sold in the United States alone 5,143,672 pounds of aspirin.<sup>3</sup> This represents a consumption of one-half an ounce (240 gm.) or 48 tablets on the average by each person in the United States annually. In the same year 3,458,009 ounces of quinine were consumed in this country.<sup>8</sup> The American people, therefore, consume about seventeen times as much aspirin a year as quinine. If, out of a group of 90,000 allergic individuals, 170 were aspirin sensitive, and 71 quinine sensitive, with only one-seventeenth as much quinine being consumed as aspirin, it would seem that the chance of a given

\* Reactions to arsphenamine occur once in 126 cases.

individual's being sensitive to quinine is at least seven times as great as the chance of his being sensitive to aspirin. These figures suggest another interpretation of the statement of Coca *et al.*<sup>1</sup> and of Prickman and Buchstein<sup>7</sup> that aspirin ranks first among allergy producing chemicals.

**Conclusions.** The increasing use of synthetic drugs of greater and greater structural complexity is undoubtedly making drug allergy one of the most important subdivisions of the field of allergy. Aspirin is a synthetic drug and is consumed in enormous quantities. It is capable of producing dangerous, even fatal reactions in sensitive individuals. Considering the number of persons who annually take aspirin, and employing quinine for a comparison, it is not thought to be, as has been claimed, the drug to which sensitization most easily develops. In fact, probably not more than 2 out of 1000 persons are sensitive to it, and of these a much smaller proportion react violently. This does not indicate the employment of less caution in the administration of aspirin to allergic persons, but it should give comfort to some, who, since the publication of Prickman and Buchstein's paper, have administered it with apprehension.

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## MOTILITY AND CHEMOTAXIS OF LEUKOCYTES IN HEALTH AND DISEASE\*

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THE resistance of a patient to bacterial infection depends in part on the activity of his polymorphonuclear leukocytes. An important function of these cells is to react to bacteria in the tissues by moving toward them, a response known as chemotaxis. Through chemotaxis, leukocytes are brought into contact with bacteria, and opportunity is given for phagocytosis and subsequent intracellular digestion.

\* This investigation was aided by a grant from the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association.

The present paper is concerned with the question, Is the movement of leukocytes toward bacteria altered by disease? If leukocytes, during an illness, move more rapidly or more directly toward the microorganisms, a greater number of cells would reach the infected area in a given time, and the patient's resistance to infection should be increased. The opposite effect would be expected if leukocytes should move more slowly or less directly toward the bacteria. Consequently it seemed of interest to measure the rate and the direction of locomotion of leukocytes from acutely ill persons and from persons not acutely ill in order to find out whether significant differences exist.

**Method.** Two groups of patients were selected from the wards of the hospital.\* In the first group were included patients who were acutely and seriously ill with such infections as pneumonia or typhoid fever, or who were suffering from acute cardiac decompensation (see Table 1). In the second group were included patients not acutely ill, most of them convalescing from chronic infections or in the hospital because of gout, malnutrition or nerve trauma (Table 2). All these patients, like those of the first group, were confined to bed.

In order to control such variable environmental factors as the time of day, the temperature of the room and the age of the bacterial culture, the observer's leukocytes (assumed to be normal) were always used as a standard with which the patient's leukocytes were compared.

A minute clump of bacteria from an agar slant was placed on a glass slide and allowed to dry, where it formed a flat, circular or oval object with a diameter of about 0.5 mm. A drop of blood obtained by puncturing the finger was placed on a coverslip and lowered on the clump of bacteria in such a way that the blood spread evenly between slide and coverslip. The preparation was sealed with petrolatum to prevent evaporation and observed with the high power of the microscope at 37° C.

By means of a drawing ocular, the image of a microscopical field containing part of the bacterial clump was projected on paper, and the position of each polymorphonuclear leukocyte in the field was recorded at intervals of 1 minute for 10 minutes, unless the cell came to rest within a shorter time. A record obtained in this way is shown in Chart I.

From such a record two values are obtained, first, the rate with which the leukocytes approached the bacteria, and, second, the rate of locomotion irrespective of direction. The rate of approach of a leukocyte to bacteria is found by measuring the dotted line  $AB$ , the shortest distance between  $A$  and the bacteria (63 mm. in the original record) and dividing by the number of minutes of observation (10). Corrected for magnification (1 mm. on the original record corresponds to 2.6 microns) the rate of approach for this cell is  $63 \times 2.6 \div 10 = 16.4$  microns per minute. The rate of locomotion is found by measuring and adding all components of the line  $AC$  (72 mm. on the original record), dividing by the number of minutes and correcting for magnification. For the leukocyte in question the value is  $72 \times 2.6 \div 10 = 18.7$  microns per minute. In this way average values were found for each record and for all the records of each patient. Details of the computation have been given in an earlier paper.<sup>3</sup>

**Results.** In most experiments the organism used to attract leukocytes was *Staph. aureus*; less often, pneumococcus or typhoid

\* The authors are indebted to the Medical and Surgical Staffs of the Hospital of the University of Pennsylvania for affording them facilities for this investigation.

bacillus, the same bacteria being used with leukocytes of the observer as with those of the patient. *Staph. aureus* and pneumococcus were tested alternately with the cells of one patient (Case 1, Table 1) and no significant difference was found in the effect of these two organisms. From present evidence it appears that leukocytes from a patient with an acute infection react to the causative organism in the same way as to other bacteria.

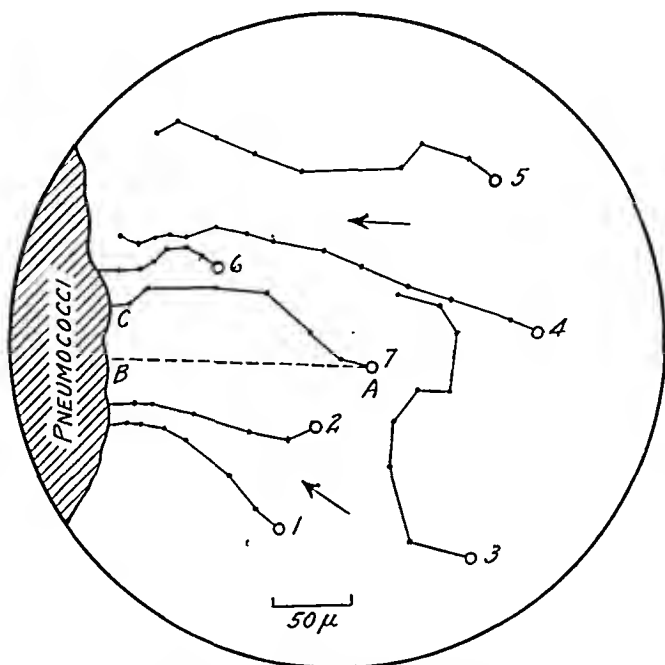


CHART I.—The reaction of polymorphonuclear leukocytes to pneumococci. Part of the clump of bacteria is shown to the left. The paths of 7 leukocytes were recorded for 10 minutes, or until the cells reached the bacteria. All the leukocytes moved toward the bacteria.

In Table 1 are given the results of experiments designed to answer the questions: Do polymorphonuclear leukocytes of acutely ill persons move toward bacteria more or less rapidly than do those of a normal person, and is there a difference in the rate of locomotion (irrespective of its direction)? Data bearing on the first question are found in the columns which give the average rate of approach of leukocyte to bacteria. Comparing values for each of the 12 patients with corresponding values for the observer, it is seen that in every instance the value for the patient was less than that for the observer, the averages for the series being respectively 9.7 and 16.1 microns per minute. That is, on the average the leukocytes of the ill person approached bacteria 40% less rapidly than did those of the observer.

The rates of locomotion, irrespective of direction, are compared

in the next columns. In each instance the patient's leukocytes moved more slowly than the observer's, the averages being respectively 14.9 and 21.1 microns per minute, a reduction of 29% in the speed of the patients' cells.

TABLE 1.—CHEMOTAXIS AND LOCOMOTION IN LEUKOCYTES OF ACUTELY ILL PATIENTS.

Case.	Diagnosis.	No. of experiments.	Bacteria used in experiments.	Rate of approach, microns per min.		Rate of locomotion, microns per min.		Chemotactic ratio.	
				Pt.	Ob.	Pt.	Ob.	Pt.	Ob.
1	Lobar pneumonia	6	Pneumococ.	9.2	13.9	15.0	18.7	0.62	0.74
			<i>Staph. aureus</i>						
2	Lobar pneumonia	2	Pneumococ.	12.0	16.3	16.6	21.4	0.72	0.76
3	Lobar pneumonia	2	<i>Staph. aureus</i>	13.9	20.3	19.8	23.9	0.70	0.85
4	Lobar pneumonia	2	<i>Staph. aureus</i>	11.1	13.2	16.7	17.9	0.66	0.74
5	Bronchopneumonia	2	<i>Staph. aureus</i>	9.7	14.0	15.6	20.9	0.62	0.67
6	Lobar pneumonia	2	<i>Staph. aureus</i>	9.4	18.7	15.1	25.1	0.62	0.74
7	Rhinosinusitis	1	<i>Staph. aureus</i>	12.4	23.9	17.2	29.5	0.72	0.81
8	Influenza	2	<i>Staph. aureus</i>	6.0	8.4	10.0	12.0	0.60	0.70
			<i>E. typhosa</i>						
9	Typhoid fever	4	<i>E. typhosa</i>	5.3	10.7	8.9	15.0	0.60	0.71
10	Therapeutic pyrexia	2	<i>Staph. aureus</i>	10.7	14.3	16.6	19.4	0.64	0.74
	Buerger's disease								
11	Acute cardiac decompensation, rheumatic	2	<i>Staph. aureus</i>	9.9	12.9	15.9	17.1	0.62	0.75
12	Acute cardiac decompensation, luetic	1	<i>Staph. aureus</i>	7.1	26.2	11.5	31.6	0.62	0.83
	Mean . . . . .	...	...	9.7	16.1	14.9	21.1	0.65	0.76

Pt., Patient. Ob., Observer.

The rate of approach of leukocytes to bacteria, their rate of locomotion and the ratio of these values (chemotactic ratio) are given for patients and for the observer. It is seen that values for patients' leukocytes were in every instance less than those for the observer.

In the last two columns are given the chemotactic ratios. These values are obtained by dividing the rate of approach by the rate of locomotion. The chemotactic ratio indicates how directly leukocytes travel toward bacteria, irrespective of the rate of movement. The ratio would be 1 if leukocyte moved straight toward bacteria, but is usually a fraction of 1 since the path is rarely perfectly direct.<sup>2</sup> In each instance this ratio is higher for the observer than for the corresponding patient.

Having thus found that leukocytes of acutely ill patients moved less rapidly and less directly toward bacteria than did the observer's, we now compared the observer's leukocytes with those of a series of patients not acutely ill. In these experiments a very different result was obtained (Table 2). It is seen that comparing column with column as described above for Table 1, there is no consistent difference between the leukocytes of the patients not acutely ill and those of the observer; the differences between the averages, as shown in the bottom row, are slight and not significant. We conclude therefore that leukocytes of the acutely ill persons moved less rapidly and less directly toward the bacteria than did those of the patients not acutely ill.



TABLE 2.—CHEMOTAXIS AND LOCOMOTION IN LEUKOCYTES OF PATIENTS NOT ACUTELY ILL.

Case.	Diagnosis.	Rate of approach, microns per min.		Rate of locomotion, microns per min.		Chemotactic ratio.	
		Pt.	Ob.	Pt.	Ob.	Pt.	Ob.
1	Pulm. tuberculosis . . . . .	13.5	13.1	16.8	18.8	0.80	0.70
2	Infect. mononucleosis . . . . .	16.6	15.6	19.5	20.4	.85	.76
3	Postop. adhesions . . . . .	9.4	7.8	14.7	12.9	.64	.60
4	Bronchitis . . . . .	20.4	15.2	25.1	17.2	.81	.88
5	Chr. brucellosis . . . . .	13.8	16.0	16.7	19.1	.83	.83
6	Gout . . . . .	13.9	15.2	21.6	21.4	.64	.71
7	Hypertrophic arthritis . . . . .	19.6	21.4	24.4	24.5	.80	.88
8	Malnutrition . . . . .	14.3	18.8	20.0	21.5	.71	.88
9	Chr. sinusitis . . . . .	14.2	8.6	19.6	14.9	.73	.58
10	Nerve trauma . . . . .	14.4	20.0	21.2	25.6	.68	.78
Mean . . . . .		15.0	15.2	20.0	19.6	.75	.77

There is no consistent or significant difference between values obtained with patient's leukocytes and those of the observer. The bacteria used were *Staph. aureus*. One experiment was made on each patient.

Using a statistical method, these conclusions were verified by comparing directly the data obtained from the two groups of patients.\*

Another observation was made in these experiments. In several instances in which the preparations were reexamined after 2 or 3 hours, great decrease in locomotion and in chemotactic response was observed in the acutely ill patient's leukocytes, whereas the observer's cells maintained their activity unimpaired. As an example is cited one of the experiments on Case 1, Table 1, a patient suffering from lobar pneumonia. When first examined, leukocytes from this patient were found to approach bacteria at the average rate of 11.0 microns per sec., and their average rate of locomotion irrespective of direction was 15.3 microns per sec. Two and a half hours later the values were respectively 4.5 and 10.3 microns per min. In contrast to the marked deterioration of these leukocytes, those of the observer during the same time declined in activity only slightly; when first examined, the rate of approach to bacteria was 14.4 microns per min., the rate of locomotion, 18.5 microns per min. Two and a half hours later, corresponding values were 11.9 and 17.3 microns per min.

Still greater functional deterioration of ill patients' leukocytes was found in other experiments. When preparations were reexamined after 2 to 3 hours, locomotion had practically ceased. A similar difference in rate of deterioration between leukocytes of ill patients and those of normal persons was noted by Philipsborn.<sup>4</sup>

\* The statistical method used was that recommended by Fisher<sup>1</sup> for dealing with small samples. Values for the rate of approach of patient's leukocytes in Tables 1 and 2 were compared. The probability that equal or greater differences between the means would occur through random sampling was found to be less than 1 in 100. The difference is therefore regarded as significant. The same probability (less than 1 in 100) was found on comparing rates of locomotion and also on comparing chemotactic ratios.

**Discussion.** It has been shown that leukocytes from a series of acutely ill persons moved less rapidly and less directly toward bacteria than did the cells in control series. Further observations have suggested that the leukocytes of acutely ill persons are relatively unable to tolerate the unfavorable conditions of experiments *in vitro*, and deteriorate more rapidly than normal cells.

In severe illness, not merely whole organs such as the heart and kidneys are depressed in function but individual cells such as leukocytes. This fact is emphasized in these experiments, which afford a quantitative measure of alteration in function of leukocytes in ill persons. The alterations in function thus established would tend to reduce the resistance of the patient to bacterial infections by lengthening the time required for mobilization of leukocytes.

**Summary.** The activity of polymorphonuclear leukocytes from a series of patients acutely ill, most of them with infections, was compared *in vitro* with that of the observer's leukocytes and of leukocytes from patients not acutely ill. Decreased rate of locomotion and less direct approach to bacteria were shown by leukocytes of the acutely ill persons. In leukocytes of some patients who were gravely ill decline in motility and chemotactic response was progressive whereas the observer's leukocytes maintained their activity unimpaired for hours. The functional changes observed would tend toward lowering resistance to infection. These experiments emphasize the fact that in severe illness the function not merely of whole organs but of individual cells is depressed, and they afford a method for quantitative measurement of changes in cellular function.

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## BOOK REVIEWS AND NOTICES

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**ARTHRITIS AND ALLIED CONDITIONS.** By BERNARD I. COMROE, A.B., M.D., F.A.C.P., Instructor in Medicine, University of Pennsylvania; Ward Physician, Hospital of the University of Pennsylvania. Pp. 752; 200 illustrations. Philadelphia: Lea & Febiger, 1940. Price, \$8.50.

THIS volume is intended to "be of practical value" to the physician. It begins with an outline for the study of the rheumatic patient and ends with a scheme for the organization of an arthritic clinic. Included between is a detailed discussion of the disease conditions embraced in the rheumatic syndrome. Each chapter is documented with numerous references to the most important literature of recent years. Chief items, diagnostic, therapeutic, indications, and contraindications, are "boxed" for emphasis. This arrangement makes for ready reference. The etiologic classification follows that adopted by the American Rheumatism Association. Various therapeutic methods are critically evaluated, and the author indicates his choice of a well rounded régime in each instance. Many of the recent "fads" are mentioned to be condemned. The hazards of gold, large doses of vitamin D, and other measures are appropriately stressed. A noteworthy inclusion is the chapter on "Spas" with a list of those which deal primarily with arthritis and their cost to the patient. The illustrations are well chosen and numerous. The format is excellent and typographical errors few. Details of the Rourke-Ernsteine sedimentation test, which is widely used in this country, are omitted. Metric doses for drugs might have been profitably added. The discussion of fibrositis seems inadequate in view of its importance in the rheumatic syndrome.

The general practitioner will find in this book the answer to the puzzling problems which arise in treating arthritis. It should receive wholehearted acceptance by the medical public and is recommended unqualifiedly. M.B.

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**DYNAMICS OF INFLAMMATION.** An Inquiry into the Mechanism of Infectious Processes. (Experimental Biology Monographs.) By VALY MENKIN, Department of Pathology, Harvard University Medical School. Pp. 244; 50 illustrations. New York: The Macmillan Company, 1940. Price, \$4.50.

THE studies of Dr. Menkin have added much to our knowledge of inflammatory reactions. In this monograph he has ably summarized his own investigations as well as the extensive literature in this field. After an historical survey of the subject he discusses the part played by the capillaries, the migration of leukocytes, the cellular sequence, and the phagocytic theory. Next, follow chapters on inflammation in relation to immunity, on the localization of foreign materials in areas of inflammation, on allergic and anaphylactic inflammation, on the rôle of lymphatics, and on inflammation and bacterial invasiveness in relation to resistance. In a concluding chapter, the views expressed are briefly recapitulated. A well selected list of 417 references is appended.

Inflammation has long been regarded the "keystone to an understanding of pathology." The reading of this book is warmly recommended to investigators and even more to practitioners.

B. L.

ÜBER DIE INTEGRATIVE NATUR DER NORMALEN HARNBILDUNG. Teils I, II and III. (Teil III. Systematischer Rückblick.) By GÖSTA EKEHORN, D.R. Med. Stockholm. Pp. Teils I and II, 1429; Teil III, 292. Helsingfors: Privately Published. Printed by Mercators Tryckeri, 1938.

THESE volumes of over 1700 pages are an extension of the author's previous monograph "On the Principles of Renal Function," published in 1931. In the first two volumes are discussed in considerable detail the experimental studies upon which is based the present-day concept of the function of the kidney; the last volume summarizes these studies. The work affords a comprehensive survey over the entire field of renal physiology, and will no doubt serve as a valuable reference book for specialists.

B. L.

**PATHOLOGICAL HISTOLOGY.** By ROBERTSON F. OGILVIE, M.D., F.R.C.P. (Edin.), Lecturer in Pathology, University of Edinburgh; Senior Pathologist, Royal Infirmary, Edinburgh; Pathologist, Deaconess Hospital, Edinburgh; Examiner in Pathology for the Triple Qualification. Foreword by A. MURRAY DRENNAN, M.D., F.R.C.P. (Edin.), Professor of Pathology, University of Edinburgh. Pp. 332; 220 photomicrographs in color by T. C. DODDS, F.R.P.S., F.I.B.P., Senior Technician, Pathology Department, University of Edinburgh. Baltimore: The Williams & Wilkins Company, 1940. Price, \$8.50.

THE purpose of this book, and the general description of its contents are so well stated by the author that we shall quote his words: "This volume is designed to act as a companion to a standard textbook of Pathology and to meet the need of the student in the class of morbid histology and of the graduate seeking more specialised knowledge in pathological processes.

"Its text is based on a series of lectures in pathological histology delivered at Edinburgh University and gives an account of the tissue-changes produced by those diseases most commonly encountered in Great Britain. Following a scheme adopted by many textbooks of Pathology the earlier chapters deal with the phenomena of degeneration, vascular disturbances, inflammation, repair and tumours, while the later chapters are devoted to special diseases of the systems. That its value might be enhanced each microscopical description is introduced by a macroscopical account of the diseased tissue or organ and, in particular instances, brief space is also given to the etiology of the condition and to the significance of the microscopical findings in relation to the nature of the disease.

"The feature of the book is the illustration of its text by 220 photomicrographs in colour."

These colored photographs are indeed very excellent, and should be much more helpful to the student than the usual black and white illustrations. The text is clear and well written. The Reviewer has no doubt that this work will prove a helpful companion to the more complete textbooks on pathology, and as such it is warmly recommended.

B. L.

**PHYSICAL THERAPY FOR NURSES.** By RICHARD KOVÁCS, M.D., Clinical Professor and Director of Physical Therapy, New York Polyclinic Medical School and Hospital; Attending Physical Therapist, Manhattan State, Harlem Valley State and West Side Hospitals, etc. Second Edition, thoroughly revised. Pp. 335; 99 illustrations. Philadelphia: Lea & Febiger, 1940. Price, \$3.25.

THE aim of the author in writing this book is to "present as concisely as possible the subject of physical therapy—exclusive of X-rays and Radium—in a manual that may be used in the curricula to enable the average nurse to assist the physician in administering treatments by physical means."

This text covers more than the essential material required by the average nurse and so provides somewhat more information than is usually given in lectures covering this subject. However, the book is simply written and is an excellent reference book for the library of all schools for nurses.

M. S.

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ON OXIDATION, FERMENTATION, VITAMINS, HEALTH AND DISEASE. (The Abraham Flexner Lectures, Series No. 6.) By ALBERT V. SZENT-GYÖRGYI, M.D., PH.D. (Cantab.), D.H.C., Prix Nobel, Professor of Medicine and Organical Chemistry, University of Szeged. Pp. 109. Baltimore: The Williams & Wilkins Company for Vanderbilt University, 1939. Price, \$2.00.

THE Flexner lectures of the Vanderbilt University Medical School are given biennially by an eminent scientist or physician within a period of two months during which he is associated with the teaching staff and the students of one department. The 1939 lectures by the Hungarian biochemist Albert von Szent-Györgyi cover the field of biological oxidations to which he has made many contributions, the best known of which is probably the isolation of an active reducing substance from the adrenal gland and from plant cells, which he later showed to be the antiscorbutic substance, vitamin C. The material is presented in a manner to inspire not only the medical students for whom it was originally intended, but anyone who enjoys a beautiful presentation of a scientific subject.

E. W.

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MANUAL OF PERIPHERAL VASCULAR DISORDERS. By DAVID W. KRAMER, M.D., F.A.C.P., Assistant Professor of Medicine, Jefferson Medical College; Assistant Physician and Chief Clinical Assistant, Vascular Clinic, Jefferson Hospital, etc. Pp. 448; 126 illustrations. Philadelphia: The Blakiston Company, 1940. Price, \$6.00.

THIS manual of peripheral vascular disorders is a timely one when new advances in this field, both in diagnosis and treatment, have come so rapidly. The author has furnished a simple and straight-forward account of the various diagnostic procedures and clinical pictures of occlusive and vasomotor vascular disorders. He has outlined the accepted methods of treatment. The procedures of oscillometry, histamine test and vasodilatation test are well presented and the author calls attention to the difference between tests for the pressure of pulsating arteries and examinations to determine the state of peripheral blood flow. The book is essentially a practical manual with few references to fundamental physiology or chemistry. The significance of tissue metabolism in relation to blood flow is not discussed. The use of heparin in thrombus and embolism is mentioned only in the treatment of the rare condition of "Essential Thrombophilia." This manual should be useful for practitioners and students of medicine. The index is complete and a good bibliography is to be found at the end of each of the four parts of the book.

N. F.

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PRACTICAL BEDSIDE DIAGNOSIS AND TREATMENT. By HENRY JOACHIM, M.D., Chief-of-Medicine, Israel-Zion and Beth Moses Hospitals; Director of Medicine, Cumberland Hospital and Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, etc. Pp. 828. Springfield, Ill.: Charles C Thomas, 1940. Price, \$7.50.

ACCORDING to the publisher: "Most differential diagnoses stress signs and symptoms. This book stresses Diseases!" This innovation in the arrangement of a text of differential diagnosis is a welcome relief from the tabulation of symptoms and signs which almost invariably led the reader

of previous decades to a wrong diagnosis. Its arrangement and content are those of a text of medicine, subject to the advantages and disadvantages of reflecting one man's experience. There are errors inexcusable in even a first edition: *e. g.*, the Hines-Brown cold pressor test is attributed to Landis, p. 207. W. J.

**BLOOD GROUPS AND BLOOD TRANSFUSION.** By ALEXANDER S. WIENER, A.B., M.D., Serologist and Bacteriologist in the Office of the Chief Medical Examiner of New York City. Second Edition. Pp. 306; 52 illustrations. Baltimore: Charles C Thomas, 1939. Price, \$5.00.

A COMPLETE and authoritative survey of an important and highly practical subject. This new edition has been brought up to date by the inclusion of much new material, as evidenced by 80 additional pages. Workers in the field will welcome this volume. R. K.

**CANCER: A Manual for Practitioners.** The Committee on Publication: GEORGE W. HOLMES, M.D., Chairman, ERNEST M. DALAND, M.D., SHIELDS WARREN, M.D., CHANNING C. SIMMONS, M.D., Editor. Pp. 284. Boston: Department of Public Health, 1940.

AN important phase of the cancer problem is the education of the practitioner in the principles of early diagnosis and in the methods of treatment which are recognized at the present time. It is almost impossible for the physician engaged in practice to keep up with the enormous current literature on malignant disease, and still more difficult for him to separate the wheat from the chaff in the reading which he is able to do. This Cancer Manual has been thoughtfully prepared in answer to this need by a committee representing the Massachusetts Medical Society and the American Society for the Control of Cancer. It contains brief articles on "Historical Trends in Cancer," "Present Trends in Cancer Research," and on general principles of diagnosis and treatment in malignant disease. The main body of the book is then devoted to consideration of malignant tumors of each anatomic region. Emphasis is placed throughout on the practical aspects of symptomatology, diagnosis, treatment, and prognosis of each type of tumor. The majority of the contributing authors are members of the faculty of the Harvard Medical School who have been active in promoting the campaign against cancer in the State of Massachusetts through the Hospitals and Clinics of the Department of Public Health and the Harvard Cancer Commission. The cancer manual which they have prepared reflects the splendid work which is being done by these organizations. The book is highly recommended to all physicians who wish to obtain a rapid review of the clinical aspects of cancer.

It is stated in the Preface that arrangements have been made to distribute this volume free to all practitioners of Massachusetts. It would be an important contribution to cancer education if a similar plan could be carried out in many other states. J. L.

**EXPERIMENTAL INVESTIGATIONS IN SERUM ALLERGY WITH REFERENCE TO THE ETIOLOGY OF RHEUMATIC JOINT DISEASES.** By EGON BRUNN, M.D. Pp. 229; 49 illustrations. Copenhagen: Einar Munksgaard; London: Oxford University Press, 1940. Price, Dan. Kr. 24.

A REVIEW of previous literature and presentation of the author's experimental evidence on the rôle of allergy in the production of the lesions of rheumatic fever and infectious osteoarthritis. By various modes of sensitizing rabbits with horse serum, the author produced joint lesions which he considers analogous to the lesions of human rheumatic diseases. He believes that his findings lend support to the view that allergy induced by

bacterial (probably streptococcal) action is the mechanism concerned in the production of rheumatic joint lesions in man. The monograph is the author's thesis for the Doctorate in Medicine at Copenhagen. R. K.

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**CHEMISTRY AND MEDICINE.** Papers Presented at the Fiftieth Anniversary of the Foundation of the Medical School of the University of Minnesota. Edited by MAURICE B. VISSCHER, PH.D., M.D., Professor of Physiology at the University of Minnesota. Pp. 296; 73 figures and 18 tables. Minneapolis: The University of Minnesota Press, 1940. Price, \$4.50.

At the celebration, in October, 1939, of the fiftieth anniversary of the foundation of the Medical School of the University of Minnesota, it was decided, in the words of the Preface, to focus the scientific program upon the single theme: "Some Trends in Medical Progress, with Particular Reference to Chemistry in Medicine." The present volume contains the papers presented on this occasion by 14 speakers, representing in equal numbers the University of Minnesota and outside scientific institutions. The diverse and interesting program included papers in the fields of colloid chemistry of membranes (H. Freundlich), osmotic work in living systems (M. B. Visscher), concentration by the kidney (J. P. Peters), vitamin chemistry (L. I. Smith), the rôle of fats in the diet (G. O. Burr), heparin and thrombosis (C. H. Best), immunity (M. Heidelberger), animal viruses (R. G. Green), sulfanilamide (P. H. Long), urinary antisepsis (H. F. Helmholz), convulsive reactivity (I. McQuarrie), analysis of nervous action (H. S. Gasser), nervous regulation of visceral processes (D. W. Bronk), and the chemical mediation of nervous impulses (W. B. Cannon). The timely nature of these subjects, the authority of the authors in their respective fields, and the generally readable and scientific, but not unduly technical, character of the contributions should gain for the volume a wide circle of readers. M. J.

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**YOUR ALLERGY, AND WHAT TO DO ABOUT IT.** By MILTON B. COHEN, M.D., Director of the Asthma, Hay Fever and Allergy Foundation, Cleveland, and JUNE B. COHEN. Pp. 177. Philadelphia: J. B. Lippincott Company, 1940. Price, \$1.50.

A TREATISE on allergy, written for laymen, in a chatty readable style that only occasionally bogs down in scientific detail. There is ample justification for such a book: allergy depends upon an inherited characteristic of the patient and may therefore manifest itself, and in a variety of clinical forms, at any time from the cradle to the grave. In at least 15% of people this involves a major clinical problem, for the solution of which the intelligent coöperation of the patient is often indispensable. Such a book will be most helpful in making such coöperation possible. R. K.

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**THE ELECTROCARDIOGRAM IN CONGENITAL CARDIAC DISEASE.** A Study of 109 Cases, 106 with Autopsy. By MAURICE A. SCHNITKER, B.Sc., M.D., Formerly Resident Physician, Peter Bent Brigham Hospital and Assistant in Medicine, Harvard University Medical School, Boston, etc. Pp. 147; 24 plates. Cambridge: Harvard University Press, 1940. Price, \$3.00.

THIS monograph includes more than its modest title would suggest. For each of the important types of congenital heart disease, there is a discussion of the clinical picture and the abnormal physiology. An earnest attempt has been made to correlate these with the electrocardiographic pattern. The material referred to consists of 109 cases, all save three with necropsy confirmation. The fact that only one abnormality (congenital dextro-

cardia) produces an electrocardiogram pathognomonic of congenital heart disease, in no wise diminishes the value of this book for one interested in the subject. The Reviewer regrets that no mention has been made of changes which may occur in the chest leads.

W. J.

**MODERN DIABETIC CARE**, Including Instructions in the Diet and the Use of the Old and New Insulins. By HERBERT POLLACK, A.B., PH.D., M.D., Instructor in Clinical Medicine, Cornell Medical College; Chief of Diabetic Clinic, Mt. Sinai Hospital, New York City, etc. Pp. 216; 13 illustrations. New York: Harcourt, Brace & Co., 1940. Price, \$2.00.

THIS volume offers no particular advantages over several excellent manuals now available. It uniquely recommends that one-third to two-thirds of the daily protein be given at the evening meal in order to provide a source of slowly available glucose throughout the night. One chapter considers the problems peculiar to the diabetic: marriage, driving, legal responsibility, occupation, and diabetic costs. Written primarily for the patient, this volume suffers from lack of illustrations; the thirteen reproduced are entirely devoted to the handling of insulin.

M. B.

**PNEUMOCONIOSIS (SILICOSIS)**. The Story of Dusty Lungs. A Preliminary Report. By LEWIS GREGORY COLE, M.D., Director of Silicotic Research, John B. Pierce Foundation, New York City, and WILLIAM GREGORY COLE, M.D., New York City. Pp. 56 and Appendix (47 pages); illustrated. New York: John B. Pierce Foundation, 1940. Price, \$1.00.

THIS small monograph is somewhat unusual. It might be described as being written in a "Colerian" style. Early in the monograph the Cole collaborators say that they have approached the study of pneumoconiosis in a manner that is not conventional. The authors describe four types of pneumoconiosis and give their reasons for their new terminology and their new classifications. The authors take issue with a number of the conventional ideas concerning silicosis and it is to be regretted that in this monograph they did not take more space to substantiate the position that they have taken concerning pneumoconiosis. One of the striking things about this monograph is the total absence of any bibliographic reference, yet throughout the text there are small numbers presumably referring to other articles published on this subject.

E. P.

**OBESITY AND LEANNESS**. By HUGO R. RONY, M.D., Formerly Associate in Medicine and Chief of Endocrine Clinic, Northwestern University School of Medicine, Chicago; Formerly Attending Physician, Cook County Hospital, Chicago, Ill. Pp. 300; 32 illustrations. Philadelphia: Lea & Febiger, 1940. Price, \$3.75.

THE delicate mechanism which controls the weight of most adults within narrow limits over a period of years has been estimated to adjust food intake and energy output to within 0.05%. This the author denotes as the "homeostatic weight regulation." In his emphasis on this nicety of balances, he diverges from the older conceptions of obesity as a disturbance of energy exchange. So far as the Reviewer is aware, the subject of leanness has not previously received extensive discussion. The volume is divided into three parts: I, A Synopsis of the Physiology of Fats and Fat Tissue, which has been called "a neglected tissue"; II, The Pathogenesis of Obesity and Leanness; and III, The Clinical Aspects of Obesity and Leanness. Modern researches on the endocrines, nervous system, and intermediary



metabolism pertaining to the problem are fully covered; speculations are carefully sifted, and short résumés are frequently appended. The lipophilia theory and a discussion of regional and segmental lipophilia are authoritatively considered. Danforth's work on the obesity of yellow mice and Davenport's data on the Mendelian inheritance of obesity receive appropriate attention. The author differs sharply with the "overeating" school and presents a relatively simple classification of both obesity and leanness. Eighty-six pages are devoted to the clinical aspects and practical details of treatment. This scholarly monograph merits the attention of investigators and should prove useful to the practicing physician.

M. B.

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**PNEUMONIA AND ITS NURSING CARE.** By HERBERT K. ENSWORTH, B.S., M.D., and LELA GREENWOOD, R.N. Pp. 177; illustrated. Philadelphia: J. B. Lippincott Company, 1940. Price, \$1.50.

A VERY comprehensive monograph that includes every aspect of medical and nursing care of the pneumonia patient today. The material for this simply written little book is based on a study of pneumonia made at Bellevue Hospital starting in 1922, financed by the Metropolitan Life Insurance Company, with additional aid from the Littauer Pneumonia Fund a few years later. In addition to the five or six hundred pneumonia patients cared for at Bellevue, other sources of information were studies made by other medical groups and articles from professional magazines, all of which are listed as references for further reading on each chapter.

M.S.

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**THE ERA KEY TO THE U. S. P. XI AND N.F. VI.** Fifth edition revised by LYMAN D. FONDA, Professor of Pharmacy, Brooklyn College of Pharmacy, Long Island University. Pp. 320. Newark, N. J.: The Haynes and George Company, Inc., 1940.

A CONVENIENT, practical, pocket-sized booklet that furnishes an epitome of the U. S. Pharmacopœia and the National Formulary, as well as information about many non-official preparations, incompatibilities, drug dosage, prescription terminology and the like.

R. K.

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**COMPLETE GUIDE FOR THE DEAFENED.** By A. F. NIEMOELLER, A.B., M.A., B.S. With a Foreword by HAROLD HAYS, M.D., F.A.C.S. Pp. 256. New York: Harvest House, 1940. Price, \$3.00.

THIS guide contains concise and authoritative information, presented in terms the average layman can understand. Separate chapters deal with the relation of colds, diet, glands, drugs, sinusitis, tonsils, adenoids, teeth, and allergy to hearing. Every aspect of impaired hearing is covered. Occupational deafness, the relation between noise and deafness, and the effects of swimming upon the hearing are given adequate attention. Audiometers, audiograms and hearing aids are explained in simple terms. Proper emphasis is placed upon re-education of residual hearing, and lip reading. The importance of voice and speech culture for the hard of hearing is demonstrated, while directions are also given for more effectively hearing the radio, conversation, the telephone and public speakers. The addition of an index will render subsequent editions more useful. This volume should be read by every deafened individual, not alone for its wealth of information (which the busy otologist only too often fails to give the patient), but also because of the understanding and sympathetic approach to the problem of social and psychologic adjustment. Most otologists will benefit by a thorough perusal of this book.

H. S.

PRINCIPLES AND PRACTICE OF AVIATION MEDICINE. By HARRY G. ARMSTRONG, B.S., M.D., Captain, Medical Corps, U. S. Army; Director, Aero Medical Research Laboratory, Air Corps Materiel Division. Pp. 504; 89 illustrations. Baltimore: The Williams & Wilkins Company, 1939. Price, \$6.50.

THAT a new specialty, Aviation Medicine, has arrived is amply attested by this timely and comprehensive volume, the first major textbook on the subject. The scope of the work is indicated by the titles of its 27 chapters: Historical; The Flight Surgeon; Evolution of Pilot Selection; Introduction to Pilot Selection; Examination of the Eye; Cardiovascular Examination; Ear, Nose and Throat; General Physical Examination; Neuropsychic Examination; Care of the Flier; Noxious Fluids and Gases; Wind, Ventilation, Cold, Heat, Light and Vibration in Flight; Effect of Flight on the Ear; Aerial Equilibration and Orientation; Airsickness; Anoxia; Acute Altitude Sickness; Chronic Altitude Sickness; Oxygen in Aviation; Psychology of Flight; Protective Flying Equipment; Aerial Relief and Sanitation. The book has been written primarily as a textbook for students and as a reference work for those actively engaged in the practice of aviation medicine. It should, however, find a much wider appeal. Written in an easy interesting style, it tells a fascinating story of the important and indispensable part that medical research has played in the development of flying. All physicians as well as scientifically minded laymen will find this volume as enjoyable reading as any best-seller. Moreover, physicians will be surprised to find much information of practical value in general medical practice, notably from the standpoint of advice to would-be airplane passengers among their patients. The book is enthusiastically recommended to all medical readers.

R. K.

A MANUAL OF OTOTOLOGY, RHINOLOGY AND LARYNGOLOGY. By HOWARD CHARLES BALLENGER, M.D., F.A.C.S., Assistant Professor of Otolaryngology, Northwestern University School of Medicine, Chicago. Pp. 302; 90 illustrations and 4 color plates. Philadelphia: Lea & Febiger, 1940. Price, \$3.75.

BASED upon the more comprehensive Ballenger's "Diseases of the Nose, Throat and Ear," this volume presents a more concise textbook by omitting theories and surgical technique while emphasizing anatomy, etiology, symptoms and treatment. It provides an adequate and reasonably priced text for undergraduate instruction, with sufficient brevity to conform to the recent trend in undergraduate teaching of the specialties. These attributes, admirably adapted to the author's purpose, render the volume inadequate as a reference work for the general practitioner and otologist.

H. S.

PRECLINICAL MEDICINE: Preclinical States and Prevention of Disease. By MALFORD W. TREWLIS, M.D., Attending Specialist, General Medicine, U. S. Public Health Hospitals, New York City; Specialist Consultant, Rhode Island Department of Public Health; Associate Editor, Medical Times. Pp. 223; 12 illustrations. Baltimore: The Williams & Wilkins Company, 1939. Price, \$3.00.

"PRECLINICAL Medicine is that branch of medicine which ascertains disease conditions which are likely to occur, such as peptic ulcer, osteoarthritis, especially the degenerative diseases. It lies wholly within the field of preventive medicine." It aims at the comprehensive diagnosis and preventive treatment of preclinical states by considering the individual as a whole, including his heredity, constitutional type, social as well as physical environment. The experienced general practitioner is not only the best prepared to work in this field, but also the one who should particularly interest

himself in it. The subject matter is presented in four sections, including (1) general considerations of history, constitution and examination, (2) specific infectious diseases, (3) non-infectious diseases (occupational diseases, diet, allergy, alcoholism), and (4) pathologic possibilities in the various parts of the body (*e. g.*, heart and blood-vessels, alimentary tract, respiratory tract and others). The chief value of the book is its viewpoint, which is deserving of the fullest consideration by physicians. The chief criticism of the book is its failure adequately to cover so broad a subject within its too limited size.

R. K.

**NEOPLASTIC DISEASES.** A Treatise on Tumors. By JAMES EWING, A.M., M.D., Sc.D., LL.D., Professor of Oncology at Cornell University Medical College, New York City; Consulting Pathologist, Memorial Hospital. Pp. 1160; 581 illustrations. Fourth edition, revised and enlarged. Philadelphia: W. B. Saunders Company, 1940. Price, \$14.00.

THE fourth edition of this great work arrives opportunely. The past 10 years have witnessed notable progress in our knowledge of neoplastic diseases, with contributions from physics, chemistry, genetics, physiology and pathology. To sift the grain from the chaff in the tremendous volume of literature thus accumulated is a momentous undertaking. The author has done this. It is, as would be expected, mainly in the section on General Oncology that most of the new material finds its place. For instance, in the chapter on Experimental Cancer Research, the work of Cook, Dodds and Hewett on carcinogenic hydrocarbons, and the chemical relationship of these compounds to hormones is included. The inclusion of new material has been accomplished without apparently increasing the size of the volume, by omitting matter of mainly historical interest, together with some controversial subjects. The book has lost none of its original value as a comprehensive survey of the neoplastic diseases; it has been brought up to date without departure from its sound and sober attitude. The fourth edition should only further increase the popularity gained by the preceding editions.

D. C.

**NOTES ON THE PREPARATION OF PAPERS FOR PUBLICATION** in The Journal of Hygiene and Parasitology. By the Late G. H. F. NUTTALL, M.D., Sc.D., Ph.D., LL.D., F.R.S., Lecturer in Bacteriology (1900-06) and Lecturer in Biology (1906-31) in the University of Cambridge, Founder and Editor (1901-37) of the "Journal of Hygiene" and Founder and Editor (1908-33) of "Parasitology." Pp. 62. Cambridge: University Press, 1940.

MEDICAL papers as they come to the editor are of three kinds: (1) Papers that have something to say and say it very well; these, all too rare, are accepted by return mail. (2) Papers that have nothing to say and say it very badly; their rejection is a pleasure. (3) Papers that have something to say, but say it very badly; they are the chief cause of editorial headache. They remind him that he really ought to write that book on the preparation of medical papers, but he puts it off, pleading the pressure of work and the pessimistic thought that those who need it most would not read it, anyway. Even Dr. Nuttall never quite got around to it in nearly 40 years of editorship, but contented himself with making voluminous notes of the advance which he gave to expert authors. After his death, Drs. G. S. Graham-Smith and D. Keilin, his successors as editors, selected and edited those of his notes which seemed likely to be most useful to many authors. The result is a little book which most writers of medical papers (and most editors) could and should read with profit.

R. K.

**HANDBOOK OF HEARING AIDS.** By A. F. NIEMOELLER, A.B., M.A., B.S. Foreword by HAROLD HAYS, M.D., F.A.C.S. Pp. 156. New York: Harvest House, 1940. Price, \$3.00.

CONTAINING a maximum of information in a minimum of space, this volume considers all types of hearing aids. It presents concise and specific information concerning the principles of operation, advantages and disadvantages, efficiency and cost of each instrument. Frank discussion and unbiased criticism enable the deafened individual to sift the maze of conflicting claims made by competing manufacturers and, with the aid of the otologist, to select the hearing aid best suited to his type of disability and to his purse.

H. S.

**SPECIALTIES IN MEDICAL PRACTICE (NELSON LOOSE-LEAF).** Edited by EDGAR VAN NUYS ALLEN, M.D., Chief of a Section in the Division of Medicine, The Mayo Clinic, Rochester, Minnesota; Associate Professor of Medicine, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. With a Foreword by DONALD C. BALFOUR, M.D., F.A.C.S., F.R.C.S. (Eng.), F.R.A.C.S., Consultant in Surgery, The Mayo Clinic; Professor of Surgery and Director, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Two Volumes. Pp. 964; 264 illustrations, 7 color plates. New York: Thomas Nelson & Sons, 1940. Price, \$25.00.

A SERIES of monographs by specialists to give such information in their respective fields as will meet the needs of the general practitioner. Subjects covered and writers are ophthalmology (Harry S. Gradle, Chicago), diseases of the ear, nose and throat (Lawrence R. Boies, Minneapolis), neurology (Henry R. Viets, Boston), psychiatry (Lloyd H. Ziegler, Milwaukee), the vitamins and vitamin deficiency diseases (Dwight L. Wilbur, San Francisco), allergy (Frank A. Simon, Louisville), orthopedic surgery (Don King, San Francisco), obstetrics and gynecology (G. D. Royston, St. Louis), endocrinology (William O. Thompson, Chicago), urology (John L. Emmett, Rochester, Minn.), and proctology (Louis A. Buie, Rochester, Minn.). A chapter on dermatology and syphilology is in preparation. The idea behind such a work is an excellent one, and it has been well carried out. The authors have largely avoided the mistake of including material involving techniques with which the practitioner should not concern himself. An exception is the section on proctology, with its descriptions of a number of formidable operative procedures. The loose-leaf principle, permitting of periodic accessions and revisions, has obvious advantages. Its chief disadvantage, excessive cost of additional material, has been minimized by the publishers, in that, instead of charging a flat yearly service fee, they offer the added material at the rate of 2 cents a page. The work should find a wide appeal.

R. K.

## NEW BOOKS

**Biochemistry of Disease.** By MEYER BODANSKY, Ph.D., M.D., Director of the John Sealy Memorial Laboratory and Professor of Pathological Chemistry, University of Texas School of Medicine, and OSCAR BODANSKY, Ph.D., M.D., Lecturer in Biochemistry, Graduate Division, Brooklyn College, etc. Pp. 684; 72 illustrations. New York: The Macmillan Company, 1940. Price, \$8.00.

**Endocrine Therapy in General Practice.** By ELMER L. SEVRINGHAUS, M.D., F.A.C.P., Professor of Medicine, University of Wisconsin, etc. Pp. 239; 49 illustrations. Chicago: The Year Book Publishers, Inc., 1940. Price, \$2.75.

*Surgery of the Hand. (Wounds, Infections and Closed Traumatata). A Book for the Practitioner and the Surgeon.* By MARC ISELI<sup>N</sup>, M.D., Surgeon, The American Hospital, Paris. Translated by T. M. J. d'OFFAY, M.B., CH.B. (EDIN.), F.R.C.S. (ENG.), Surgeon and Deputy Medical Superintendent, City General Hospital, Leicester, and THOMAS B. MOUAT, M.D., CH.M. (EDIN.), F.R.C.S. (ENG.), Surgeon, The Royal Infirmary, Sheffield, Lecturer in Surgery, The University of Sheffield. Pp. 353; 135 illustrations, including 8 plates. Philadelphia: The Blakiston Company, 1940. Price, \$5.50.

*The Head and Neck In Roentgen Diagnosis.* By HENRY K. PANCOAST, M.D., Late Professor of Radiology and Director of the Department of Radiology, University of Pennsylvania, EUGENE P. PENDERGRASS, M.D., Professor of Radiology and Director of the Department of Radiology, University of Pennsylvania, and J. PARSONS SCHAEFFER, M.D., PH.D., Professor of Anatomy and Director of the Daniel Baugh Institute of Anatomy, Jefferson Medical College. Pp. 976; 1251 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, \$12.50.

*Simplified Diabetic Manual with 163 International Recipes (American, Jewish, French, German, Italian, Armenian, etc.).* By ABRAHAM RUDY, M.D., Associate Physician and Chief of the Diabetic Clinic, Beth Israel Hospital, Boston; Instructor in Medicine, Tufts College Medical School, etc. Introduction by DR. FREDERICK M. ALLEN. Pp. 216; illustrated. New York: M. Barrows & Co., Inc., 1940. Price, \$2.00.

*Pneumonia and Its Nursing Care.* By HERBERT K. ENSWORTH, M.D., Instructor in Medicine, Cornell University Medical College; Clinical Assistant Visiting Physician, Second (Cornell) Medical Division, Bellevue Hospital, New York City, and LELA L. GREENWOOD, B.A., R.N., Supervisor of Medical Pavilion, Bellevue Hospital, New York City; Assistant Instructor, Department of Therapeutics, New York University Medical College. With a Foreword by RUSSELL L. CECIL, M.D. Pp. 177; illustrated. Philadelphia: J. B. Lippincott Company, 1940. Price, \$1.50.

*Health is Wealth.* By PAUL DE KRUIF. Pp. 246. New York: Harcourt, Brace & Co., 1939. Price, \$2.00.

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# PROGRESS OF MEDICAL SCIENCE

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## PREVENTIVE MEDICINE AND EPIDEMIOLOGY.

UNDER THE CHARGE OF

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### THE EPIDEMIOLOGY OF MUMPS.

WITH much of the world turned to war and the remainder variously engaged in recruiting military strength, epidemiology steps forward into obligations long associated with armed conflict. As a consequence, ordinary epidemiologic interests undergo appreciable and sometimes startling changes in emphasis. Typhus fever becomes a matter of unusual concern; memories of the 1918 pandemic of influenza are freshened; but most surprising of all to the uninitiated is the consideration given to mumps.

To the military surgeon, mumps is no passing indisposition of benign course but ranks with many of the more formidable diseases because of its frequent appearance in epidemic proportions, the high non-effective rate among army personnel brought about by the long indisposition, and because in young adults the associated manifestations of epidemic parotitis lead to a clinical course considerably more serious than when mumps is a disease of childhood. In summarizing the general problems that communicable disease presented in the war of 1918, Haven Emerson<sup>18</sup> stated that in terms of sick wastage, and measured by the number of days lost from military service on account of sickness, mumps was the most important disease in the American Expeditionary Force in France. Indicative that opinion has not changed in the course of years, is the recent statement of Surgeon General Parran,<sup>66</sup> of the United States Public Health Service, that next to the venereal diseases, mumps is the most disabling of the acute infections among recruits.

Aside from military considerations mumps warrants interest in its own right. The practicing physician, to be sure, is usually occupied with diseases of more serious course and higher fatality, so that mumps by more or less common consent is relegated with chickenpox, rubella, and some other infections to a group designated the minor communicable diseases. However, the biologist faces no distinction between

major and minor infections, and the epidemiologist often derives equal profit, in respect to the fundamental laws of behavior of communicable processes, from diseases that are common and benign.

The current interest in virus diseases has led to a number of studies on the specific infectious agent of mumps, with the result that the past few years have seen notable additions to what was known of the etiology, biologic nature, and mode of origin of this condition, with promise of more effective measures for clinical management and control.

**The Clinical Disease.** Mumps is such an old disease and so many good descriptions are available,<sup>62,65</sup> that the clinical aspects will be touched upon only insofar as they pertain to interpretation of the mechanism of the disease process.

The use of the term epidemic parotitis for statistical purposes and as descriptive of the disease is unfortunate, for it associates the condition too closely with changes in the parotid. The current edition of the *International List of Causes of Death*<sup>39</sup> catalogues the disease as mumps, which should bring about more general usage of a time-honored name favored by most clinicians and epidemiologists.

The clinical recognition of mumps is ordinarily so certain in comparison with many other infectious diseases that not much confusion is introduced into epidemiologic interpretations through inclusion of other forms of parotitis or conditions which simulate parotitis but are not inflammations of that gland. They furthermore occur so uncommonly as to have little influence on morbidity statistics. That is not true, however, of mortality rates. Mumps of itself is rarely a cause of death, but some of the conditions confused with it often end fatally.

Mumps is unattended by suppuration, but suppurative parotitis does occur in connection with septicemic and cachectic states, and in association with diseases such as typhoid fever and scarlet fever. The fatality in such instances is likely to be great, not so much because of the involved parotid but because of the primary condition. Post-operative swelling of the parotids, especially after surgical procedures involving the abdominal cavity, and symptomatic parotitis occurring toward term in pregnancy are not rare. A chronic recurrent form of parotitis is associated with diseases of the upper respiratory tract, like the recently reported instance<sup>5</sup> of a series of recurrent attacks of parotitis, one of which was mumps. Prolonged swelling of the parotid may be due to secondary infection after mumps, or in exaggerated instances and very rarely to Mikulicz's disease. An experience with 367 hospital admissions<sup>25</sup> for mumps is presented in Table 1.

Such a distribution would not be typical of private practice, since only the more severe and more difficultly determinable infections are ordinarily sent to hospital.

The development of knowledge about mumps falls readily into three periods. The first was concerned chiefly with the study of frank epidemics, and served to establish the communicability of the condition and its wide distribution. Hirsch's<sup>37</sup> collection of some 150 epidemics occurring between 1714 and 1859 showed the disease to be prevalent from Iceland to Egypt, and from Alaska to Polynesia. Accumulated evidence from outbreaks in the first half of the nineteenth century illustrated another epidemiologic feature of mumps, its predilection for prisons, orphanages, boarding schools, garrisons, and ships. The second



general advance was concerned with better definition of the clinical features of mumps for which especial credit is due the sustained interest of a brilliant line of French army surgeons. The third era was initiated with the production of mumps experimentally and the recognition of the specific infectious agent.

TABLE 1.—PATIENTS REFERRED TO HERMAN KIEFER HOSPITAL AS MUMPS, DETROIT, MICHIGAN, 1927-1937.

Disease.	Cases.	Incidence per 100 cases.
Mumps . . . . .	310	84.5
Local suppurative processes of head and neck . . . . .	27	7.4
Other infectious diseases with complications suggesting mumps . . . . .	20	5.4
Suppurative parotitis . . . . .	5	1.4
Symptomatic parotitis . . . . .	3	0.8
Contusion of face . . . . .	1	0.3
Mikulicz's disease . . . . .	1	0.3

**Etiology.** The long series of bacteriologic investigations on saliva, blood and tissues from patients with mumps, starting with the early studies of Capitan and Charrin<sup>7</sup> and continuing for many years, led to the demonstration of various pyogenic cocci but to no satisfactory proof that they had anything to do with the production of the disease. They were ordinary mouth contaminants or the factors in secondary infection.

A spirochete reported by Kermorgant<sup>44</sup> to be the specific agent of mumps never received much credence. The parotitis produced in monkeys could not be transmitted in series. Pontano<sup>68</sup> found the suspected spirochete more often in normal saliva than in that from patients with mumps, and Rocchi<sup>75b</sup> proved it to be only a banal inhabitant of the buccal cavity.

The experiments of Granata<sup>28</sup> in 1908 gave the first suggestion that the cause of mumps was a filterable virus. Rabbits injected intravenously with bacteriologically sterile filtrates of saliva from patients suffering from mumps had fever over a period of 3 days. Direct inoculation of the parotid glands of rabbits with filtered saliva gave rise to a swelling considered to be mumps, but the many subsequent failures to produce experimental mumps in the rabbit suggest the interpretation to have been erroneous.

Nicolle and Conseil<sup>61</sup> in 1913 injected fluid aspirated from the parotid gland of a patient with mumps, directly into the parotids of several monkeys. One animal developed what was considered a typical swelling of the gland, accompanied by fever and a monocytosis of the blood.

Four of the 10 monkeys that Gordon<sup>26</sup> injected intracerebrally with bacteria-free filtrates of mumps saliva developed meningeal symptoms on the fourth day and died. Necropsy showed a sterile lymphocytic meningitis, but attempts to transfer the infection to other monkeys were unsuccessful. An additional monkey inoculated intraperitoneally and intravenously became ill after an incubation period of 7 days and showed swelling of the parotid glands.

With filtered mouth washings from patients with mumps, Wollstein<sup>99a,b</sup> inoculated directly the parotid glands of half-grown cats, producing a swelling resembling mumps in man after an incubation

period varying from 5 to 8 days. The condition was reproduced in series. The virus was obtained most readily from the saliva of patients in the first 3 days of the disease, less readily on the sixth day, and not at all on the ninth. It was present in the blood of patients having marked constitutional effects. A mild aseptic meningitis of 3 to 5 days' duration,<sup>90c</sup> and transmissible in series, was induced by intrathecal injection of filtered saliva from early mumps, while sterile saliva from normal persons gave no reaction.

Complete and convincing demonstration that the infectious agent of mumps is a filterable virus came in 1934. Johnson and Goodpasture<sup>43a</sup> injected into the lumen of Stenson's duct of monkeys a fresh untreated saliva from patients in the early stages of the disease. Acute non-suppurative parotitis, analogous to that of mumps in man, and dependent histologically on a primary degeneration and necrosis of the parenchyma cells of the parotid, followed 4 of 6 attempts, the 2 failures being with saliva taken on the third day and later. Filtered mumps saliva had the same effect, although the incubation period was somewhat longer than the 6 to 8 days observed with unfiltered material. Recovery from the experimental infection conferred immunity to reinoculation for at least 3 months. The saliva of persons without mumps produced no disease. Since the materials used were free from demonstrable microorganisms, including spirochetes, they believed the causative agent of mumps to be a filterable virus.

Appreciating that final proof of causal relation must depend on production of the specific disease in the natural host with virus from the experimental disease, experiments were undertaken with 17 volunteers,<sup>43b</sup> children living in a small town, 4 of whom were presumably immune and 13 susceptible to mumps, with none known to have been recently exposed to the disease. The virus, in a suspension of minced parotid gland from the eleventh monkey of a passage series, was sprayed on the buccal mucosa and instilled into the nostrils, this being repeated the following day. The 4 immune persons were unaffected. Six of the 13 supposedly susceptible children developed clinical mumps, 3 had doubtful infections, and 4 failed to react. Saliva from one of the definite infections produced non-suppurative parotitis in a monkey. The incubation period for experimental mumps of man was, however, from 18 to 33 days in contrast to the 6 to 8 days in the monkey where virus was instilled directly into the parotid duct. These experiments established the cause of mumps to be a filterable virus, which now has been passed in monkeys through 35 generations in 3 years.

Important confirmation came from Findlay and Clarke<sup>20</sup> in England, who initiated the disease in monkeys with filtered mumps saliva and passed the virus in series with production of typical experimental mumps. Observation of suggestive virus particles by fluorescence microscopy in smears from the nose and throat of mumps patients contributed little evidence one way or the other.<sup>84</sup> In France a simple and rapid method was developed for collecting appreciable amounts of saliva directly from the opening of Stenson's duct.<sup>81</sup> Levaditi and his associates<sup>54</sup> also produced experimental parotitis in monkeys and in the chimpanzee, and confirmed their results histologically. Transmission in series was accomplished, but with some difficulty. No effect followed intravenous injection of filtered mumps saliva nor instillation

of the material into the nasal fossæ of monkeys. Contact of an infected chimpanzee with a healthy animal did not serve to transmit the disease. Because the experimental infection remained localized in the single parotid injected, since signs of a general infection were indefinite, and because similar histologic changes although of lesser degree were believed to occur after injection of presumably inert and non-specific substances, the French workers held certain reservations about the demonstration of a definite and constantly active virus, although agreeing that some element in the saliva of mumps could be transmitted in series through monkeys with the production of non-suppurative parotitis.

The real difficulty came from the fact that the histologic changes taking place in man in the course of mumps are not known definitely. Death from mumps is rare, necropsies still fewer,<sup>48,93</sup> and biopsies most infrequent. Occasional records such as those of Delater<sup>34</sup> caused Levaditi to remark, however, that the lesions of experimental mumps corresponded remarkably with the changes which had been noted in the human. Rocchi<sup>75a</sup> has reviewed current information about the histopathology of mumps in man, and Johnson and Goodpasture<sup>43d</sup> described in detail the pathologic changes of experimental mumps. Whether the lesions of experimental parotitis produced by injection of mumps filtrates into Stenson's duct of monkeys are microscopically specific, or are non-specific and reproducible by the injection of various other substances is capable of experimental proof; which Bloch<sup>2</sup> proceeded to acquire by showing the fundamental lesion of experimental mumps to be a focal acinar necrosis involving all or most of the cells of an acinus, a reaction not associated with injection of inert or other infectious substances.

**Pathogenesis.** With mumps demonstrated to be a virus disease and with an acceptable method for its production experimentally, there is opportunity for an improved understanding of the pathogenesis and biologic nature of the disease. A goodly amount of desirable information is still not at hand, but sufficient exists for examining the situation in the light of current developments, and for correlating much information of more remote origin, possible now of other interpretation than sometimes originally made.

The first and probably today the most commonly entertained conception of mumps is that of a primary local disease of the parotid which arises from invasion of the buccal cavity, progression of the infectious agent along Stenson's duct and eventual production of a non-suppurative swelling of the gland. The less common clinical manifestations of mumps such as orchitis, oöphoritis, pancreatitis, and the disturbances of the central nervous system, are thought to be complications of the primary disease brought about through occasional penetration of the agent into the blood or lymph stream.

Others regard mumps as a general rather than a localized process, with entrance of the virus by nose or mouth, lodgment on the mucous membranes of the nasopharynx probably, penetration to the blood stream and thereafter localization in various glandular structures, especially the parotid; and sometimes also in the central nervous system through successful penetration of the blood-brain barrier.

More recently has come the concept of Philibert<sup>67</sup> that mumps is due to a virus both cytotropic and neurotropic and comparable to that

of rabies; that it penetrates the host tissues by some unknown route, possibly the conjunctivæ; and electively gains entrance to the brain, provoking secondarily more or less reaction of the meninges. The virus being of low virulence, only slight and transient lesions are ordinarily produced; if more active, the virus may accomplish destruction of the nerve cells, giving rise to clinical encephalitis and occasionally paralyses. The virus is subsequently eliminated by the salivary glands, perhaps by nerve pathway, with swelling and partial destruction of the parotid; by the pancreas; or passes within the testicle which it often destroys in part; or into the kidney or other structures. Mumps is thus visualized as a primary disease of the central nervous system followed by secondary localization in salivary glands, pancreas, and testicle.

Since a satisfactory understanding of pathogenesis has so direct a bearing on programs for control, evidence will now be sought from known facts about the mechanism of spread of this filterable virus, from the immunity reactions which follow infection, from the clinical behavior of the disease, and from the studies of experimental mumps, in support of one or other of the concepts just stated.

**Spread of the Virus.** The sole reservoir of mumps infection appears to be man. An occasional reference to the natural disease in the dog<sup>69</sup> receives no confirmation from attempts to transmit infection from animal to animal by contact, or from man to animal. Experiments have invariably failed even with the chimpanzee,<sup>54</sup> and common epidemiologic knowledge discounts more than the accidental occurrence of such an event.

*Mumps Carriers.* Whether the human reservoirs of infection are limited to persons manifestly ill, or whether latent and subclinical infections also have a part, rests on no certain evidence. Practical experience in epidemics would indicate that latent infection with production of the temporary carrier state<sup>24</sup> is a factor, an impression also held by Zinsser.<sup>101</sup> Understanding subclinical infection to indicate disease with minimal clinical reaction and always measurably below recognized classical manifestations, such instances have been reported many times as far as the parotitis is concerned; in the form of slight tenderness at the angle of the jaw or slight redness at the orifice of Stenson's duct in association with mumps encephalitis.<sup>94</sup> Conceivably, the same situation could exist independently of other localizations, remaining wholly unrecognized as mumps infection.

Evidence of another kind comes from field surveys of history of previous attack by communicable disease<sup>33,86</sup> in general populations. Mumps occupied a somewhat intermediate position—64%<sup>10a</sup>—between measles, which had affected more than 89% of persons by age 20 years, and diphtheria with 10%, the latter a disease with a definitely known carrier factor in its epidemiology. Annual case rates adjusted for age<sup>10b</sup> show the same relationships<sup>10c</sup> between these diseases. The basic data about mumps would be expected if anything to be more accurate than those for measles. With no reason to believe that the two viruses are not equally widespread, one explanation of the difference in case rates could be the frequency of manifest disease as distinguished from latent or subclinical infection.

*Mode of Transmission.* The usual method of transmission is by direct contact and probably by droplet infection with perhaps occasional

instances where mumps results from oral contact with an article recently contaminated with the saliva of a patient with mumps.<sup>95c</sup>

*Portal of Entry.* The principal portal of entry would seem to be by way of the mouth or nose. Johnson and Goodpasture<sup>43b</sup> have produced mumps in man experimentally by spraying the virus on the mucosa of the upper respiratory tract; while Philibert's<sup>67</sup> suggestion of entrance by the conjunctivæ is wholly speculative. Whether the virus thereafter proceeds directly by way of the parotid duct or penetrates the mucosa to reach the parotid indirectly by the blood or by nerve trunks is not known. Angina frequently marks the early stages of the infection,<sup>60</sup> this condition often being overlooked because it ends at about the time that parotitis appears. This has been interpreted as the first localization of the virus.

Experimental mumps of monkeys<sup>43a</sup> after instillation of the virus directly into the duct had an incubation period of 6 to 8 days. The same virus after 11 passages in monkeys had an incubation period of 18 to 33 days when sprayed on the mucosa of the upper respiratory tract of man. With allowance for differences in host species and a possible attenuation of the virus by animal passage this would suggest that direct infection by the duct was an effective but probably not the natural method of infection, which if indirect would presumably involve a longer incubation time.

Examining histologically a piece of tissue from the parotid of a child in the third day of mumps, de Lavergne, Kissel, and Leichtmann<sup>53</sup> found no evidence of an ascending infection and inclined to the belief that infection was descending and came to pass by way of vessels or nerves.

*Period of Infectiousness.* Drawing on his own experience and a meticulous review of the literature, Wesselhoeft<sup>95b</sup> came to the conclusion that the usual incubation period of mumps was 18 days, with considerable variation from this mean in both directions. Orr<sup>64</sup> found a periodic fluctuation in numbers of cases every 18 days through 6 successive waves in an army outbreak in England; and thus another kind of evidence suggests that 18 days is about the correct period.

The incubation period is not wholly innocuous, for mumps becomes communicable some 48 hours before swelling of the parotid<sup>55</sup> is noted, and about 24 hours in advance of the first symptoms, at which time it reaches its height. Johnson and Goodpasture<sup>43a</sup> were unable to find virus in the saliva after 3 days of mumps, Wollstein<sup>99b</sup> in some few instances on the sixth day, but not on the ninth. This information is the guide to more logical regulations for isolation and quarantine than are now often prescribed.

*Communicability.* Field experience indicates that a rather solid contact is necessary for contracting the infection of mumps, such as that between members of a household or repeated and close contact under other situations. As with all communicable diseases, a number of epidemiologic considerations influence the degree of communicability; but by and large, given approximately equal and similar conditions, mumps is a good deal less communicable than measles and chickenpox, is less communicable than whooping cough, and much more communicable than scarlet fever and diphtheria.

**Immunity.** The resistance conferred by an attack of mumps is usually life-long and is just as enduring after unilateral as after bilateral parotitis, the prevalent notion to the contrary notwithstanding.<sup>95c</sup> Information from experimental mumps of the monkey<sup>43c</sup> corroborates this clinical experience, in that parotitis of one side invariably gives immunity to subsequent inoculation of the opposite gland, indicating that immunity is general and not local. Nevertheless, repeated attacks of mumps have been reported and in some instances may involve the side opposite the first.

Anyone experienced in communicable disease hospital practice appreciates the considerable error in histories of common communicable diseases of childhood, both in respect to diseases that persons have had and those that they have not had. If second attacks of mumps be limited to instances where both attacks were seen by a competent observer and if confusion with suppurative parotitis is eliminated,<sup>5</sup> second and recurrent attacks would be found not very common. Second attacks are expectedly more frequent in army practice where the elapsed time between attack in childhood is long, where the degree of exposure is great, and because of such general factors as stress and crowding and perhaps a carrier factor not otherwise materially pertinent.

A significant feature of Johnson and Goodpasture's<sup>43c</sup> studies on experimental immunity in the monkey was the demonstrated existence of subclinical and latent infections and their activity in producing immunity. Clinical mumps never followed spraying of the virus into the oral cavity of monkeys, but a solid immunity was frequently demonstrated thereafter as tested by direct inoculation of the virus into the parotid duct, a process which regularly induces mumps in the susceptible animal. A single injection intracerebrally was regularly followed by immunity, although clinical evidence of cerebral or meningeal disease was wholly absent and the virus could not be passed in series. Attempts to immunize monkeys passively to subsequent intraparotid injection of virus showed human convalescent serum to possess some weak antiviral action, but the experiments lacked preciseness because of readily appreciated technical difficulties. In general, the monkey appears relatively more resistant to the virus of mumps than is man.

**Clinical Considerations.** Turning now from those features of the spread of the virus in nature and the immunity reactions which follow natural and experimental infection, as they bear on the question of pathogenesis, the clinical behavior of the disease itself will be examined in the search for further evidence about the manner in which mumps develop.

Mumps is, of course, a good deal more than a simple disease of the parotid glands. The involvement of the associated salivary glands, the gonads, the pancreas, the central nervous system especially, and a number of other structures, including the special senses, has been recognized for many years and adequately described. The frequency with which these conditions occur is well illustrated by the recent reports of Janbon<sup>41a, b, 42</sup> and many others. Their place in the pathogenesis of the disease is not so well established, being variously interpreted as complications following parotitis; a part of a general infection of which parotitis is only another manifestation; as capable of inde-

pendent existence; or that some one of them represents the primary disease to which the others, including parotitis, are secondary.

*Time and Frequency Distribution.* The weight of clinical evidence assures that, with rare exceptions, only the mature testis and ovary are involved in mumps infections. The frequency of orchitis among mumps patients past puberty is appreciably great—from the earlier review of Wesselhoft<sup>95a</sup> and the more recent summary by Stengel,<sup>85</sup> in the nature of 18%. While orchitis usually follows parotitis and is more often unilateral than bilateral, there can be no doubt from the observations of many clinicians that it can also precede the appearance of parotitis, occur simultaneously, or exist as the sole clinical manifestation. The origin of the manifestation is probably hematogenous.<sup>85</sup> As long ago as 1899, Edwards<sup>17</sup> reported 4 patients with primary involvement of the testis, of whom 3 later had parotitis and 1 did not. Waddelow<sup>91</sup> records primary epididymitis in mumps. Wesselhoft<sup>95a</sup> collected 30 reports of orchitis preceding parotitis, and no less than 64 cases of orchitis without parotitis; and increasing numbers have been added since the date of his review.

Ohlmacher<sup>63</sup> describes the much rarer circumstance of oöphoritis preceding parotitis. A laparotomy performed on the third day of an acute illness revealed a normal appendix, but the right ovary was considerably enlarged in comparison with the left, and presented a few minute petechiæ. Three days after operation the young woman developed a typical double parotitis of mumps.

Pancreatitis is only an occasional, or at least a much less commonly recognized effect in the course of mumps,<sup>34</sup> although Greene and Heeren<sup>29</sup> found 7 in their series of 100 young adults with mumps. The important consideration is that it follows the same pattern of behavior<sup>3,9,87</sup> as does involvement of the gonads, in that it may precede, accompany, or follow the swelling of the salivary glands.

No good statistical information is available concerning the frequency of encephalitis as a manifestation of mumps in a general population. The numbers in many series are too small for satisfactory judgment. Other groups represent selected ages, commonly young adults, and especially soldiers; and some data were collected at a time when clinical appreciation of the condition had not reached its present level. Indicative of reported experience under military conditions is a frequency of 9.8% in Dopter's<sup>16</sup> French army series of 1910 and 1911; to be compared with the single case of encephalitis among 5756 mumps patients at Camp Wheeler<sup>71</sup> in 1918. In a civilian outbreak of some 2500 cases<sup>60</sup> in Portland, Oregon, the frequency of encephalitis was 0.6%, while Steinberg<sup>83</sup> reports an incidence of 10% for 210 cases.

When encephalitis appears as a part of the picture of mumps it is usually as an aftermath of parotitis,<sup>59</sup> at varying intervals of 2 to 10 days. Outspoken involvement of the central nervous system as the initial manifestation of mumps infection, to be followed later by parotitis, is no unusual occurrence, Silver<sup>77</sup> having collected a series of 21 such cases. The recent report of Gasser<sup>22</sup> is particularly informative because mumps encephalitis was observed in its full period of development before parotitis, the patient having been under hospital observation for a traumatic injury. Sometimes encephalitis and parotitis develop concurrently.<sup>47</sup>

*The Occurrence of the Several Manifestations of Mumps as Independent Processes.* The great preponderance of clinical mumps has parotitis as the sole manifestation. If the other clinical conditions that make up the total disease have parity with parotitis as evidences of secondary localization after an initial general infection—presumably of the blood—or after some other primary localization, then the expectancy is that in some instances each will also exist independently of the others, as does parotitis. Accumulated clinical experience shows this to be true. Orchitis presumably of mumps origin and without an associated parotitis is a matter of long observation.<sup>95a</sup> Similarly, encephalitis independent of other manifestations of mumps has been reported by Howard,<sup>38</sup> and by Wallgren,<sup>92</sup> among others, while Wesselhoeft<sup>95c</sup> offers evidence of like behavior in respect to pancreatitis. Identification as of mumps origin has invariably depended upon clinical and epidemiologic evidence, since the virus of mumps has never been isolated under such circumstances, other than from parotitis.

*Evidence of a General Infection.* The appearance of a swollen parotid may be the first accident in the course of well-being, but more frequently swelling of the gland is preceded by functional and general signs of variable intensity which correspond to the beginnings of a general infection, Moutier<sup>60</sup> emphasizing especially a constant angina, and Greene and Heeren<sup>29</sup> the frequent occurrence of an enlarged spleen.

*Latent Encephalitis.* Philibert's<sup>67</sup> concept of mumps as a primary disease of the central nervous system evolved from the many clinical observations on the associated meningo-encephalitis. This condition invariably shows a well-marked pleocytosis of the cerebrospinal fluid. Many years ago, however, Monod<sup>58</sup> reported increased numbers of lymphocytes in the cerebrospinal fluid from 6 of 8 patients who had parotitis but no demonstrable signs of meningeal irritation whatsoever. Of 40 patients with mumps at the Willard Parker Hospital,<sup>21</sup> 10 with clinical encephalitis and 6 with only parotitis had cell counts that ranged from 15 to 880. That pleocytosis of the cerebrospinal fluid occurs in the absence of clinical signs is assured; the difference of opinion lies in its frequency, with estimates varying from an uncommon occurrence,<sup>70</sup> 5%,<sup>8</sup> the 25% of Teissier and Eismen,<sup>62</sup> to a constant presence as indicated by the results of de Massary,<sup>55a, b</sup> and associates who routinely examined the cerebrospinal fluid of 56 soldiers with mumps, 40 having no clinical evidence of encephalitis. All showed increased numbers of lymphocytes some time during the course of the disease, although not always in the fluid drawn from the first puncture.

In an attempt to relate these disturbances to the virus of mumps, de Lavergne<sup>51a, 52</sup> and associates injected filtered and unfiltered cerebrospinal fluid from patients with mumps encephalitis into the subarachnoid space of rabbits by suboccipital puncture. Essentially no clinical reaction followed, which was also true when the fluid was introduced into the parotid, the testicle, or the blood stream. However, the number of lymphocytes in the cerebrospinal fluid increased significantly, to be followed later by histologic evidence<sup>51b</sup> of a demyelination of perivascular distribution. A variety of inert materials, including spinal fluid from other sources, failed to give these changes, nor did filtered saliva from non-mumps patients. Attempts to neutralize the supposed virus *in vitro* were unsuccessful, nor could active immunity



after one injection be determined. Moreover, the changes noted were almost invariably produced by cerebrospinal fluid from patients with simple mumps,<sup>51a</sup> in the complete absence of signs of encephalitis or cytochemical alteration of the spinal fluid. The cerebrospinal fluid of a number of persons was next examined 15 days<sup>51c</sup> after exposure to mumps, and 3 to 7 days before parotitis appeared. The typical reaction of the rabbit followed. Fluids from some of the contacts who failed to develop parotitis nevertheless produced the same reaction in the rabbit as did those who later developed the disease, suggesting an inapparent infection of the central nervous system as the only manifestation of mumps infection in man. de Lavergne and Kissel<sup>50</sup> believe these experiments bring support to the hypothesis of Philibert. The matter hinges on the soundness of the criteria considered indicative of the activity of a mumps virus. Experimental parotitis was never produced with the spinal fluid of patients or of infected rabbits.

**Biologic Nature of Mumps.** Drawing now on the various kinds of evidence which have been offered in an attempt to formulate a tenable explanation of the pathogenesis of mumps, it would appear that the portal of entry is by the nose and mouth,<sup>43b</sup> with lodgment of the mumps virus on the mucosa of the upper respiratory tract.<sup>60</sup> A variety of evidence, epidemiologic, clinical, immunologic and experimental, indicates mumps to be a general infection,<sup>60</sup> probably of the blood stream,<sup>99a</sup> and not a strictly local disease. In the localizations that follow the general infection, the virus manifests a special predilection for glandular structures of which the parotid is most often and first affected. With multiple structures involved, the parotid usually precedes all others, but sometimes this sequence is disturbed with striking effect on the timing of the disease, so that the testes, the central nervous system or the pancreas may be first invaded. The infrequent occurrence of clinical neurologic disease, the special selectivity of the virus for glandular tissues, and the preponderance of encephalitis over meningeal reaction suggest that if this part of the disease is related to the virus of mumps it comes about through passage of the agent through the blood-brain barrier. It is not necessary, of course, to assume that the march of the disease follows one route only. The three possibilities noted may all act, but the evidence suggests that just outlined as usual.

That mumps is a primary disease of the central nervous system is an interesting hypothesis. Certain clinical features are suggestive.<sup>11</sup> Histologically Johnson and Goodpasture<sup>43c</sup> found some evidence that infection of nerve tissue after intracranial injection of monkeys may spread by nerve to the otic ganglion and possibly the parotid—at the same time emphasizing the need for further experiment. However, a direct relation between the virus of mumps and the naturally associated encephalitis has not been established.

**Endemicity and Epidemicity.** Mumps is an endemic disease in general urban populations, but subject to irregular fluctuations of incidence beyond the established norm, uncommonly reaching epidemic proportions other than in areas or institutions where crowding favors transmission of the virus.

Gundersen's<sup>30</sup> experience in Norway and that of Ringberg<sup>73</sup> in Denmark illustrate admirably the secular variations in the incidence

of mumps, an excess prevalence occurring roughly every 7 or 8 years. Much the same behavior has been evidenced by mumps in the United States Army, other than for the abnormal factor of wars<sup>90a</sup> (Fig. 1). Definite outbreaks sometimes occur in rural regions but the true epidemic potentialities of the disease are best manifested in military populations.

*Seasonal Fluctuations.* Mumps can occur at all times and in all places, but under endemic conditions a regularly increased incidence occurs in winter and spring, especially during the months of March and April;<sup>12b</sup> and some three-quarters of epidemics occur at this time.<sup>78</sup> The incidence drops to very low levels during the summer. No better explanation of the seasonal variation in prevalence of mumps can be offered than is possible for other common communicable diseases. To the usual considerations of weather and closer contact in winter months comes a suggestion that physiologic changes in the host may be a factor. For 3 successive years, Johnson and Goodpasture<sup>43c</sup> were forced to interrupt their studies on experimental mumps of the monkey because of inability to induce the clinical disease with any degree of regularity from July through September, although using virus suspensions which they had every reason to believe were satisfactory.

*Host Distribution.* In civilian life and under ordinary conditions sex has no influence on susceptibility to mumps.<sup>19</sup> The reported differences in racial incidence<sup>90b</sup> seem to be dependent more upon opportunities for infection than upon genetic influences. For example, in the World War the rate for mumps among white enlisted men was 49.99 per 1000 and for colored troops 134.75, a fact which finds partial explanation at least in the reported statistics from Alabama<sup>82</sup> from 1926 through 1934, where the rate for colored is 10.4 and for white persons 31.3 per 100,000. In an Indian boarding school Tillim<sup>89</sup> observed an attack rate of 90 %.

The commonest age of attack is at about 6 years. In Massachusetts,<sup>12b</sup> 88.6 % of reported cases involve children less than 15 years of age.

*Mortality Rates.* Death rates for mumps are extremely low—0.12 per 100,000 over a period of 22 years in Massachusetts<sup>12a</sup>—and apparently even less than official records indicate. Investigating reported deaths from mumps in the state of New York, Williams<sup>98</sup> found many instances where the diagnosis was questionable. Some 20 of 65 patients who died had some variety of suppurative disease. Relatively few fatal infections were at the ages of greatest prevalence. An appreciable number of the patients who died were more than 65 years of age or infants, age groups with very low attack rates which would indicate a degree of severity much greater than clinical experience suggests.

*Military Outbreaks.* The influence of wars on epidemics of mumps<sup>4</sup> comes from the excessive recruiting of troops, so that large numbers of susceptibles are brought together at the same time. This factor is well illustrated by the continued high morbidity for mumps in the French Army, several fold greater than in the British Army. It is reasonable to suppose that the same proportion of recruits come from rural and urban districts but because of compulsory military service in the French Army larger numbers serve for short periods, with a consequent rapid turnover, in contrast to the long enlistments that characterize the British Army.

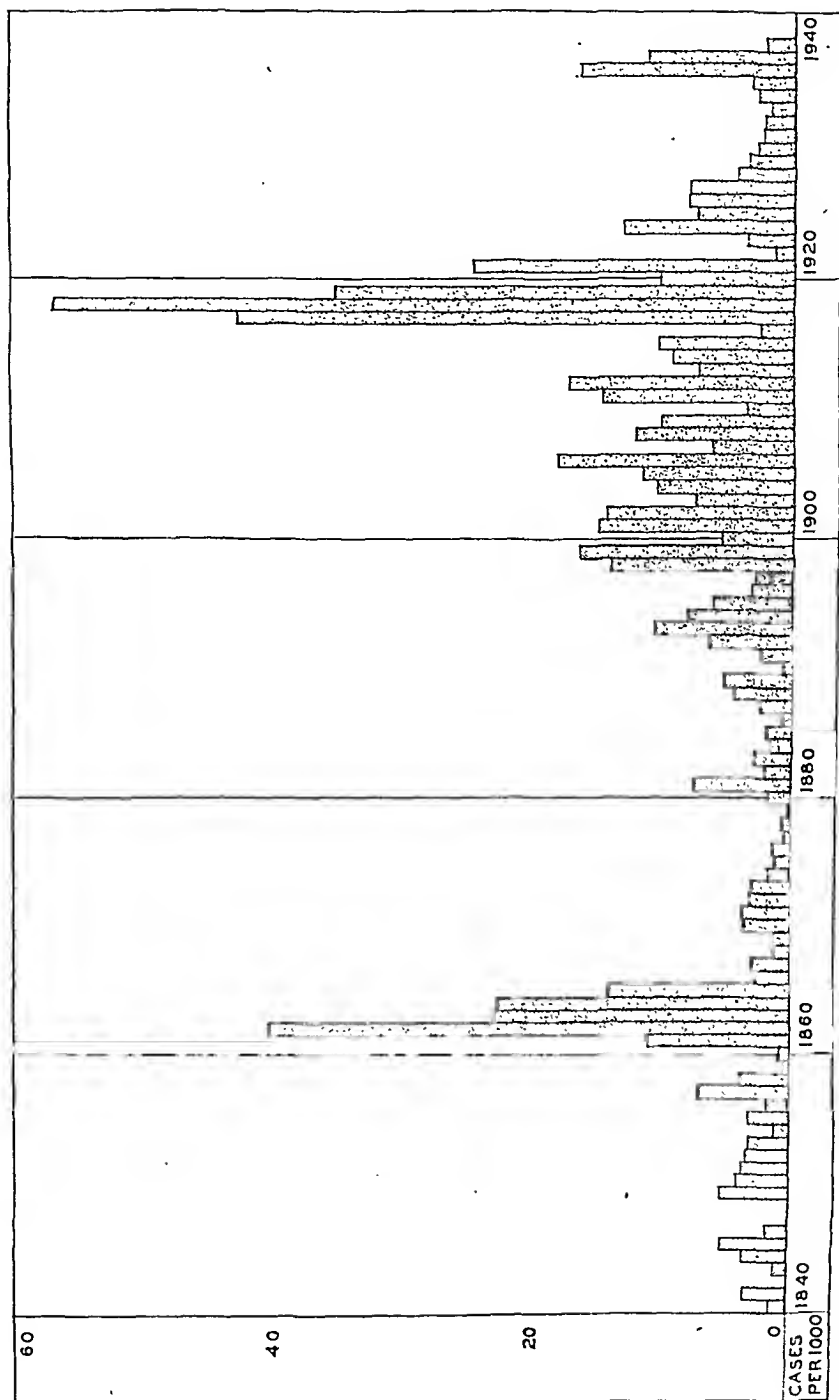


Fig. 1.—Attack rates for mumps, white troops of the United States Army, 1840 to 1938, lacking 1842, 1847 and 1848.

In the American Army, great epidemics of mumps occurred in both the Civil War and during the World War of 1918, with no marked disturbance during the course of the Spanish-American War, since mobilization took place in late spring and summer, and additions to the army did not extend into the mumps season. The importance of this factor is emphasized by Cook<sup>13</sup> who found that men entering the navy in the fall and winter months suffer a much higher incidence of cerebrospinal fever during the first year than those entering during the spring and summer. The extreme susceptibility of recruit, for contagious diseases in general is brought out by Wheelis,<sup>96</sup> who showed that by far the highest rates occur during the first 2 months of service, and that this holds true for all seasons, although less marked in summer than in winter.

During the World War mumps was more prevalent in large camps than in smaller and less densely populated organizations; and attack rates were directly related to whether troops were drawn from the rural South, or from industrial regions like the Eastern and New England states. In some instances attack rates were unusually great, 32% in Camp Wheeler.<sup>71</sup> In the course of recent years, attack rates in American Army practice have been about 10 per 1000,<sup>90a</sup> while civilian rates for all ages, in a state like Massachusetts, were 1.8 per 1000. Of course, reporting is much better in the army; Hedrich's<sup>32</sup> correction indicating that only about 12% of cases are officially notified in Massachusetts.

**Administrative Control.** Lacking a method for permanent protection, or satisfactory measures for treatment of the more serious manifestations which so frequently occur at a later age, attempts to prevent mumps in the individual exposed child of 5 to 15 years are under ordinary circumstances not advisable.

Susceptible children exposed at home may return to school 3 days later, this interval accounting for delayed symptoms from simultaneous exposure. Exclusion from school then follows from the fourteenth through the twentieth day, immune children continuing attendance. In our experience, quarantine of contacts has served to limit outbreaks in schools, hospital wards, and institutions more effectively than for almost any other of the common communicable diseases of childhood.

Isolation of patients with mumps is sometimes practiced for unreasonable periods, as long as 21 days. Laboratory experiment and field experience show that communicability rarely extends longer than the duration of the swelling; which makes at least 7 days' isolation, and until the swelling of the salivary glands has receded, a good general recommendation, sometimes necessarily extended by late appearance of a second involved gland.

The extensive outbreaks of mumps that so often occur in quickly mobilized troops could conceivably be avoided by not concentrating recruits from rural regions, but mingling newly enlisted men from city and country to give a mixture of immunes and susceptibles. A practice in communicable disease hospitals applicable to troops is to enter on the service record a note of previous attacks of communicable disease<sup>23</sup> which forms a basis for quarantine and aids in the diagnosis of doubtful infections. Once an outbreak is well under way, quarantine is essentially useless under military conditions because of the numerous and repeated contacts. Furthermore, it interferes with military activities so greatly, that it is only justified in the attempt to curb an incipient

outbreak. Daily inspection of known immediate contacts for early manifestations of the disease aids in prompt isolation. The measures outlined are equally applicable to fixed populations under civil conditions.

**Specific Prevention.** The serum of patients convalescent from mumps is used under special circumstances to prevent the disease, and has been recommended as a measure for modifying or eliminating the severer effects that tend to follow the initial parotitis.

The usefulness of the method is restricted by the short protection afforded, and the limited availability of the serum. It finds application for children in poor health or suffering from other diseases;<sup>76</sup> in avoiding the disorganization of activities that follows an outbreak of mumps in summer camps;<sup>88</sup> in hospital outbreaks;<sup>31,72</sup> in boarding schools;<sup>100</sup> and under military conditions or in institutions<sup>6</sup> where an outbreak is recognized early with promise of successful control.

Although whole blood was first used<sup>35</sup> for passive protection and has been employed by some others,<sup>1</sup> the separated serum is more practicable because it can be stored for use as required. Blood is preferably collected 2 to 3 weeks after clinical attack, but 3 months is satisfactory and more remote infections serve in necessity. The usual dose is 10 cc. administered intramuscularly, although some have used 20 cc. and others as little as 3 cc.

The manner in which mumps spreads and the short period of infectiousness before clinical recognition suggest that prompt use of convalescent serum should give encouraging results, which is corroborated by a considerable personal experience with outbreaks in hospital wards and institutions, and is an opinion held rather broadly.<sup>45,97</sup> Skrotsky,<sup>79</sup> for instance, observed that 177 of 179 exposed susceptibles escaped infection; Kutscher<sup>46</sup> in a summer camp for boys aged 9 to 16 years protected all but 1 of 52 who had not had mumps.

The administration of convalescent serum to patients with clinical parotitis, in an effort to prevent other manifestations of the disease, lacks proof of any worthwhile value. Some reports are of individual cases<sup>27,67</sup> and other series<sup>36,49</sup> are brief and inadequately controlled. The difference of 20% and 29% for orchitis in Iversen's<sup>40</sup> series of treated and untreated patients lacks statistical significance. If the method has any value it should come from immuno-transfusion<sup>16</sup> of large amounts of blood. However, most of the evidence obtained in the laboratory by means of animal experiments and tissue cultures<sup>74</sup> points to the fact that once a virus has attached itself to a cell or passed within a cell, antibodies in the therapeutic serum encounter great difficulty in reaching them in effective doses.

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ORIGINAL ARTICLES.

THE MEDICAL AND SOCIAL APPROACHES TO THE PROBLEM  
OF CHRONIC RHEUMATISM.\*

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**History.** Chronic rheumatism is perhaps the oldest of all known diseases. In the Museum of the University of Kansas is the skeleton of a large swimming reptile, the mosasaurus, whose foot is said to show the lesions of chronic rheumatism. The beast is supposed to have lived 600,000,000 years ago. The Ape Man of the Pliocene period, a mere 2,000,000 years old, the Java and the Lansing men, our own ancestors of only 500,000 years ago, had chronic rheumatism of the spine and so did the Predynastic Nubians<sup>24,33,37</sup> and ancient Egyptian mummies of 8000 years before Christ, and the pre-Columbian Indians of America. We are back in the United States.

The name of these protean diseases, chronic rheumatism, is derived from the Greek word *ῥεύμα*, meaning humor. The shade of Galen still stalks; it challenges us to find the solutions of the problems which these diseases still present, but as we tackle them we may perhaps take heart by remembering the aphorism of William the Silent, "It is not necessary to have hope to begin nor success to persevere."

**Incidence.** Chronic rheumatism seems to be much more prevalent in the Temperate Zones than in the regions near the Poles or the Equator. Its incidence is greater in chill, damp climates than in high and dry regions, but it is a wellnigh universal disease.

The State Department of Public Health in 1930 made a survey of the incidence of chronic disease in Massachusetts the population of which is about 4,250,000. It was estimated that 6500 years of work and nearly \$8,000,000 worth of wages are lost every year

\* The Nathan Lewis Hatfield Lecture of the College of Physicians of Philadelphia, delivered May 1, 1940.



in this small state because of the ravages of chronic rheumatism. Rheumatism was the greatest single cause of chronic disease in Massachusetts.<sup>4a</sup> The National Health Survey of 1935 and 1936<sup>25</sup> seems to prove that of the chronic diseases "rheumatism," including in that term, arthritis, gout, "neuritis," "neuralgia," "lumbago" and probably "fibrositis," stands first in prevalence, first as the cause of disability (if mental cases be excluded), second as to permanent invalidity, but only fourteenth as a cause of death. As Bigelow and Lombard say,<sup>4b</sup> "Rheumatism then cripples in the largest number of cases and kills in the smallest. This very ability to cripple without killing would seem to put it in the lead of all other chronic diseases as of preëminent social, economic and medical importance." The social implications of this statement are evident. The editors of the Fifth Rheumatic Review well say, "Thus by all accounts 'rheumatism' is still the chief contender for the title of 'King of Human Misery.'"<sup>20</sup>

CHART 1.—ESTIMATED PREVALENCE OF SPECIFIED CHRONIC DISEASES IN THE UNITED STATES (1937).

Disease.		No. of cases.							
		0	1	2	3	4	5	6	7
Rheumatism . . . . .	6,850,000								
Heart diseases . . . . .	3,750,000								
Arteriosclerosis and high blood pressure	3,750,000								
Nephritis and other kidney diseases . .	1,550,000								
Nervous and mental diseases . . . . .	1,450,000								
Cancer and other tumors . . . . .	930,000								
Tuberculosis—all forms . . . . .	680,000								
Diabetes mellitus . . . . .	660,000								

The relative importance of chronic rheumatism may be appreciated when we compare its prevalence with the incidence of several of the other common chronic diseases. The incidence of heart disease proper is only about one-half that of chronic rheumatism. The same may be said of arteriosclerosis. There seem to be more cases of chronic rheumatism in the United States today than the sum total of all those persons affected by cancer, diabetes and all forms of tuberculosis early and late.

**Medicine's Attack on the Problems of Chronic Rheumatism.** Physicians must have recognized *ῥέυμα* before medical history began, for we know that Hippocrates made an attempt to differentiate what Radulphe later called "gout" from chronic rheumatism. Men dreaded its inroads before the Christian era. With Gaius Catullus they prayed, "Save me, oh, save me, from this vile disease."

Sydenham in 1683 differentiated chronic rheumatism not only from gout but also from rheumatic fever. Heberden (1782), Haygarth (1802), Charcot (1853), Robert Adams (1857), the two

Garrods, A. B., the father (1859) and Sir Archibald E., the son (1890), Bannatyne (1896), Pribram (1902), Goldthwait (1904),<sup>17</sup> Hoffa and Wollenberg (1908), all studied carefully the clinical pictures of these diseases and added to our biochemical and pathologic knowledge of it. In 1906, however, T. S. P. Strangeways,<sup>38</sup> Lecturer on Special Pathology in the University of Cambridge, England, was able to open the first Research Hospital for the study of chronic rheumatism. Six years later he had accumulated notes on 4000 cases of rheumatoid arthritis and assembled in a small museum 2000 specimens of arthritic joints.

The greatest increment of knowledge was furnished by the beautifully illustrated monograph of Nichols and Richardson on "Arthritis Deformans," published in 1909.<sup>26</sup> This gave us the first clear and convincing picture of the essential morbid tissue changes associated with what we now call atrophic or rheumatoid arthritis and hypertrophic arthritis or degenerative joint disease. The work of these investigators has never been gainsaid. The more recent work of Allison and Ghormley<sup>2</sup> and other pathologic research, based on a greater material and carried out with more modern methods of tissue study, have given us more details and confirm the original work of Nichols and Richardson.

The active interest of internists and practitioners grew very slowly. The arousing and maintenance of the interest of medical men is, to a very large extent, due to the work of one of your Fellows, Dr. Ralph Pemberton.<sup>28</sup> I believe that to him more than to any other man we owe the sustained renaissance which has occurred in the study of chronic rheumatism.

The renaissance continues abroad and at home. Before the onset of the European War there were 27 branches of the International League for the study of rheumatic diseases in Europe and in the continents of North and South America. The Sixth Congress of the Ligue Internationale was held in London and Oxford and Bath in 1938. Plans were well under way to hold the Seventh Congress, under the presidency of Dr. Pemberton, in Philadelphia, New York and Boston in June, 1940. In times of peace we shall look forward with pleasurable anticipation to the completion of our plans.

The Lovett Foundation in Boston helped materially by grants from the Department of Public Health of Massachusetts and by the Commonwealth Fund, the Rackham Arthritis Research Unit of the University of Michigan, and many special arthritic or rheumatic clinics all over the country for the study and treatment of these diseases, are constantly adding to our knowledge and bringing surcease to their patients. There are at present two journals devoted to rheumatism in England. The British Rheumatism Committee also frequently issues bound volumes reporting significant clinical and laboratory research. Six American reviews of English and American medical literature dealing with the rheumatic diseases

have been published and are models of thoroughness and in the value of their editorial comment. We have found "hope to begin" and perhaps may be said to have had a little success in persevering.

**Classification of Chronic Rheumatic Diseases.** I fancy we should all agree that the most helpful classification would be one based upon etiology. Our present lack of knowledge as to specific causes of these diseases forbids such a classification. For the moment we may be content with a "working" classification and perhaps the one suggested by this chart may be as useful as any. Most of our serious medical and social problems are to be met in dealing with the two (possibly three) most common types in which the exact etiology may be said to be unknown.

#### CHART 2.—WORKING CLASSIFICATION OF ARTHRITIS.

##### I. Origin known:

1. Traumatic, *e. g.*, due to internal derangements of joints, fractures into joints, etc.
2. Infectious, *e. g.*, due to tubercle bacillus, gonococcus, streptococcus, staphylococcus, etc.
3. Neuropathic, *e. g.*, due to tabes, syringomyelia, leprosy, etc.
4. Arthritis associated with metabolic or constitutional diseases, *e. g.*, hemophilia, gout, etc.
5. Anaphylactic or allergic, *e. g.*, associated with serum sickness.
6. "Fibrositis," "fascitis," tenosynovitis, etc., of known origin.

##### II. Origin not certainly known:

1. Rheumatoid, proliferative or atrophic arthritis.
2. Hypertrophic, degenerative or osteoarthritis.
3. Rheumatic fever.
4. "Fibrositis," "fascitis," tenosynovitis, etc., of unknown origin.

To an increasing majority of trained and open-minded observers, it seems almost certain that chronic rheumatism of the atrophic or rheumatoid type and chronic rheumatism of the hypertrophic or degenerative joint disease type are distinct and separate diseases. Virchow apparently believed them to be different manifestations of a single syndrome and grouped them under the name of "arthritis deformans." As they both do deform the joints, the casual medical observer remains satisfied with the name. We shall do well not to close our minds to the possibility that many similar etiologic factors may influence the onset of both diseases. For the betterment of both, many similar therapeutic methods are applicable.

We are of the opinion that there are many reasons for believing that "Still's disease" or "Feltz's syndrome" associated with lymphoid hyperplasia, represents only a rather rare manifestation of atrophic or rheumatoid arthritis occurring in children. Many careful observers have reached the conclusion that the condition variously designated as spondylitis deformans, Marie-Strümpell syndrome, *spondylose rhizomelique* or *spondylose ankylopoietica* is also only a somewhat unusual form of atrophic or rheumatoid arthritis the chief manifestations of which are commonly confined to the spine. Your speaker inclines to the belief that spondylitis deformans may yet be found to represent a third distinct syndrome of

chronic rheumatism. We will not labor the point but simply call attention to its peculiar lesions, especially of the almost constant ossification of the anterior common ligament of the spine and to the fact that whereas atrophic or rheumatoid arthritis affects women much more often than men, spondylitis deformans attacks men much more often than women in a ratio variously estimated from 1 in 5 to 1 in 10.

**Etiologic Concepts.** We shall attempt to discuss the etiologic concepts which have influenced the treatment of these diseases in the past and those which obtain at present.

**Diathesis.** The hand of the Lord was first believed to be the chief cause of chronic rheumatism. Alas, many physicians still have a strong tendency to incriminate the Lord. The *ῥέυμα* or humoral theory of Galen is dead, but the almost equally vague theory of a rheumatic diathesis persists and cannot yet be completely denied.

**Infection.** Since Pasteur's discovery of microbes the infectious theory has been widely accepted, strengthened chiefly by the articles of Billings<sup>5</sup> and Miller in 1916, of Burbank and Hadjopoulos in 1925,<sup>6</sup> of Cecil, Nicholls and Stainsby in 1929,<sup>8a</sup> and of Small in 1930.<sup>36</sup> It has been held that even in the absence of frank "rubor, calor and dolor," the essential etiology of acute and even chronic rheumatism could be explained by the existence of not only evident but also hidden foci of infection. The most common habitats of these foci were thought to be the teeth, the tonsils, the sinuses, the gall bladder, the genito-urinary and the alimentary systems. The theory of focal infection is not a new theory, for we find the physician of Ashur-bani-apal, King of Assyria, in the seventh century before Christ, giving his master the following advice: "He will speak the truth with the king as the king demanded: the pain in his head, his sides and his feet has come from his teeth, they must be extracted." The brilliant work of Cecil and his colleagues,<sup>8b,27</sup> in connection with the positive agglutination reactions to hemolytic streptococcus obtained from a very high percentage of the sera of atrophic or rheumatoid cases, convinced them that some form of streptococcus was the usual causal agent. However, Dawson, Olmstead and Boots,<sup>12</sup> after confirming Cecil's agglutination reactions and admitting their strong etiologic suggestiveness, were unable to evaluate the *significance* of these findings. Tillett, Abernethy and Fisher<sup>39</sup> had called attention earlier in this same year to the fact that sera derived from patients acutely ill with various bacterial infections are capable of reaction to certain strains of hemolytic streptococci. Several investigators have reported high percentages of positive findings of streptococci in the blood and joints of atrophic or rheumatoid patients. Many other careful laboratory workers have been unable to confirm these findings and the number of the negative results seems to be on the increase. Chapman and his associates,<sup>9</sup> after what seems to have been careful research, consider that "an

analysis of the theoretical basis for and the practical tests of serologic and immunologic reactions which have been proposed for determining which organisms have invaded the tissues of a particular person suspected of having chronic infection indicates that each method is subject to error."

In a recent article Reimann and Havens<sup>32</sup> even question the reliability of the focal infection theory itself. They point out the fact that patients suffering from chronic rheumatism (especially from atrophic or rheumatoid arthritis) are usually subnormal before the disease begins, or become so as a result of the disease. They believe that the focal infections which may be discoverable, very possibly result from their lowered resistance and, therefore, may be interpreted as effects rather than as causes. The probability is suggested by the frequent disappearance of these foci, if and when, the recovery of, or the remission from, the underlying chronic disease occurs.

From the point of view of an orthopedic surgeon I hope that this informed and considerate article will have a wide circulation. Such a presentation has been long overdue. Seeing more patients in the later rather than in the earlier stages of their disease, I have for many years been made aware that although most of them had had teeth and tonsils and many important internal organs taken away, their arthritis remained and paradoxically often seemed unlike their incomes to have been augmented by their losses. Today there remains little informed opinion to support the belief that either active or slumbering infection plays any leading rôle in the initial etiology of hypertrophic or degenerative joint disease, though any active infection may often make the joint symptoms temporarily more acute in both types.

*Gastro-intestinal Factors.* Deficiency diets and gastro-intestinal disorders probably have an indirect etiologic connotation because they may fertilize the body soil for a crop of arthritic joints. Holbrook,<sup>21</sup> whose experience has been large and whose observations are keen, reports that the majority of his patients with atrophic or rheumatoid arthritis give a history of gastro-intestinal dysfunction and constipation. They present sigmoids which are frequently redundant and colons which are often tortuous with areas of spasm in an otherwise atonic bowel.

*Trauma.* Hypertrophic or degenerative joint disease may be said to be often initiated by trauma and in both this disease and in atrophic or rheumatoid arthritis, macro- and especially the micro-traumata of use are among the chief causes of increase of troubles.

Bauer and Bennett,<sup>3</sup> after many years of research into the nature of hypertrophic or degenerative joint disease, have been led to believe that it results from the wear and tear of increasing age and repeated trauma and is not the result of an inflammatory process, metabolic process or endocrine dysfunction. Because articular

cartilage has little or no power of regeneration they believe that this type of chronic rheumatism can never be completely "cured," but that certain measures may be instituted which will either arrest or slow the progress of the degenerative changes. They recognize the fact that extensive degenerative changes can be present in an individual without necessarily causing any important joint symptoms.

*Possible Endocrine Factors.* We shall discuss later these newer etiologic possibilities and merely mention them here.

*Emotional Etiologic Factors.* Every keen experienced student of chronic rheumatism from Charcot<sup>10</sup> to Cobb<sup>11</sup> has been made aware of the possibility of neurologic and psychologic etiologic factors as predisposing and possibly precipitating causes of atrophic or rheumatoid arthritis. Cobb, Bauer and Whiting,<sup>11</sup> writing in 1939, conclude that "environmental stress, especially poverty, grief and family worry, seem to bear more than a chance relationship to the onset and exacerbation of rheumatoid arthritis." This investigation was carefully controlled and included a considerable consecutive series of cases. For many years we have been made conscious of the existence of these etiologic factors, and believe that closest attention should be given them, especially since Cannon has been able to connect emotional disturbances intimately with both functional disturbances of the body systems and with eventual organic lesions. Lucretius Titus Carus,<sup>7</sup> in the last century, B.C., was aware of this emotional factor and of its organic possibilities.

"Then be it ours with steady mind to clasp  
The purport of the skies, the laws behind  
The wandering courses of the sun and moon;  
To scan the powers that speed all life below;  
But most to see with reasonable eyes  
Of what the mind of what the soul is made  
And what it is so terrible that breaks  
On us asleep or waking in disease."

*The Etiologic X Factor.* Before we leave the subject of etiology we must refer to perhaps the most important of all etiologic concepts. This is the unknown factor which we know exists but which we have thus far been unable to discover. The chances are better that it will prove to be a biochemical rather than a bacterial factor. For many decades it has been occasionally observed that when certain patients affected by atrophic or rheumatoid arthritis had an attack of jaundice, their joint symptoms frequently almost completely disappeared, very rarely permanently, but often for periods of many weeks or months. It has been known for many years also that when a woman with atrophic or rheumatoid arthritis becomes pregnant, both her objective and subjective joint symptoms markedly improve, to return usually in more aggravated form shortly after

she is delivered. A similar but less impressive train of events often follows a surgical operation and even a simple ether anesthesia.

As far as we are aware, no such remissions occur under such circumstances in the course of hypertrophic or degenerative joint disease. Hench<sup>19</sup> suggests that there may be a factor common to these occurrences in jaundice and pregnancy. Closely related are such diverse substances as cholesterol (which increases during pregnancy), ergosterol (the precursor of vitamin D), some of the sex hormones, cortin and bile acids. All these substances contain the phenanthrene nucleus.

So far we do not have the answer to the question, why do remissions of symptoms in atrophic or rheumatoid arthritis occur often with jaundice and almost always during pregnancy? We may be reckless enough to venture certain guesses before concluding the paper. At present we stand "at attention" before the mystery, "looking and listening," but the train of events which will bring us the good news of discovery is still on the way and alas, behind time.

**Therapeutic Trends.** Generalized disease: One therapeutic trend overshadows, we may say dominates, all others. It is based on the conviction that chronic rheumatism is a generalized disease analogous to lues, tuberculosis, "Bright's disease." It is not a disease of the joints *per se*, although the joints become diseased.

1. GENERAL MEASURES. *Early Recognition.* Successful therapy demands early recognition and early treatment.

*Team Play.* We emphasize the importance of "team play." A competent and interested internist is the first essential. He must be the captain of the patient's fate and chart his course, but since the conservation of joint function is a prime desideratum, a knowledgeable bone and joint specialist should be his first mate. Other mates may be required, and physical therapists and perhaps psychiatrists, but they must all be "mates" under one captain.

*Rest.* Rest of body and mind is another essential. This does not mean inactivity, indeed it often means more exercise, in order to conserve joint function and avoid emotional strain.

*Body Mechanics.* I must give testimony to the faith that is in me with a few words on the subject of body mechanics as a universally applicable method of the general treatment of a generalized disease. No sculptor or painter ever successfully portrayed a healthy or efficient person who did not exhibit in either activity or repose good body mechanics, or a weak depressed person who did not exhibit faulty posture. William James, the psychologist, once said that the erect posture exerted an important effect upon the emotions. We might have expected this great student of the mind to have said that the emotions exert great influence upon posture, which is to some extent true, but he did not. If we see to it that our rheumatic patients lie and sit and walk in such a manner that the great systems of the body, respiratory, gastro-intestinal, muscu-

lar and skeletal, may function with the smallest amount of mechanical restriction, we shall remove one of the most serious handicaps to their physical and emotional betterment.

2. SPECIFIC MEASURES. *Diet.* There is no standard diet for chronic rheumatism. As Minot has said, we must seek to find the optimum diet for each individual, optimum in caloric value, in quality and in vitamins. Pemberton<sup>29</sup> has destroyed Haige's shibboleth of the proscription of meat and has demonstrated that a diet high in proteins, fat and vitamins and low in carbohydrates very often tends to represent an optimum diet.

There has been much healthy "debunking" of "constipation;" yet we must not neglect obviously faulty alimentation, represented perhaps quite as frequently by too rapid passage of food as by intestinal stasis. I am old-fashioned enough still to believe that it is as important to make sure that the ashes of the food we eat do not contain too many clinkers as it is to keep the cylinders of our motor cars free from carbon.

We shall perhaps need soon a little "debunking" of vitamin "cure alls." Articles have appeared stressing the importance of vitamin D and there has been more or less "drug house" urge to employ massive doses, but Abrams and Bauer,<sup>1a</sup> after careful trial and observation, have concluded that the use of large doses of vitamin D in the treatment of atrophic or rheumatoid arthritis is of little or no value and that there is insufficient proof that massive doses may not be harmful. Recent reports suggest that the various vitamin B compounds may have a wider application in very considerably larger dosage than they have been often administered. We know how important adequate amounts of vitamin A and vitamin C have been proved to be.

*Vaccines and Sera.* The widely accepted theory of focal infection as an important etiologic factor has led to the common employment of vaccine therapy. End-result studies have been disturbingly confusing. It is perhaps fair to say that the reports of their therapeutic value have become less "rosy" in direct ratio to the carefulness of investigation. The recent paper of Sidel and Abrams,<sup>34</sup> read at the 1939 meeting of the American Rheumatism Association, entitled "Treatment of Chronic Arthritis—Results of Vaccine Therapy With Saline Injections Used as Controls," casts grave doubts as to the specific nature of the method. A very considerable number of cases of both atrophic or rheumatoid arthritis and of hypertrophic or degenerative joint disease were included in their studies which seem to have been very carefully controlled. Their conclusions may be summarized by saying that judged by objective and subjective improvement in the condition of the joints and in enhanced ability to work, the injections of vaccines were of no more therapeutic value than the injections of normal saline solution.



*Drugs.* Since we have no specific drug for chronic rheumatism, we may group the ones in most common use under the old-fashioned headings of sedatives, analgesics, vasodilators and certain drugs which are thought to be useful but the exact action of which we do not know, *e. g.*, sulphur and the salts of gold. It is needless to name the sedatives. These are well known and different physicians have different favorites. The safest analgesics still seem to be the new and old salicylate preparations which are also vasodilators. The more definitely vasodilating drugs such as erythrol-tetranitrate and arsenic, which is thought to influence favorably not only the blood flow but the nature of the blood itself, are often beneficial in the hands of a wise internist who employs them with caution as a whip and spur. The influence, if any, of the formerly frequently prescribed iodides is probably due to their stimulation of thyroid activity.

The knell of the much publicized treatment of chronic rheumatism by sulphur seems to have been rung by the investigations of Freyberg, Block and Fromer<sup>15</sup> and the studies of Abrams and Bauer.<sup>16</sup> The conclusions from both these very thorough and well controlled pieces of research are almost identical to the effect that there is no evidence to suggest that a sulphur deficiency or any abnormality of sulphur metabolism exists in patients with arthritis and that there is no biochemical or metabolic indication of need for, or benefit from, sulphur medication in the treatment of arthritis.

There is more to be said for gold therapy, popularized by Forestier,<sup>14</sup> although as far as we are aware the only well-controlled and to some extent end-result study of the administration of gold salts which has been published is that of Ellman and Lawrence<sup>13</sup> published in 1938. There is much literature on the subject. Hartfall, Garland and Goldie<sup>18</sup> in 1937 reported very favorable results of gold therapy administered to 900 cases of atrophic or rheumatoid arthritis. Nearly 10% they described as "cured" and nearly 57% as greatly improved. We should here remember Kalmeter's end-result studies of cases treated in the Rheumatic Clinics of Sweden without the use of gold, which showed 60% of the patients back on their old jobs and 18% requiring no more pensions when reviewed 3 years after they had been discharged from the hospitals. In the Ellman and Lawrence series, numbering 52 cases, only typical cases of atrophic or rheumatoid arthritis, whose ages ranged from 18 to 68 years were selected. The control group of 20 received intramuscular injections of bland almond oil; the second group of 16 received injections of small doses of Solganol B; the third group of 16 received larger doses of Solganol B. The dangers were recognized and patients with existing kidney damage were excluded. Their results after 9 months' study and two courses of gold therapy are interesting and suggestive.

Of the control group of 20, 1 lost all signs of the disease and 13

were improved; none became worse. Of the group of 16 receiving small doses of gold salts, 6 lost all signs of the disease, 8 were improved, but 1 became worse. Of the group of 16 receiving large doses of gold salts, 8 lost all signs of the disease and 7 were improved, but 1 became worse. The changes in the sedimentation rate were striking. A normal sedimentation rate was attained in 28% of the controls, in 43% of the group receiving small doses of gold and in 72% of the group receiving large doses.

On the other side of the ledger stands the record of toxic reactions. One fatal case occurred in the gold series from agranulocytosis associated with purpura hemorrhagica and in 43% of the cases treated with gold a stomatitis occurred, which in 4 of the gold-treated cases was very severe, very persistent and very painful. In over 18% of the gold-treated cases squamous and exfoliative skin eruptions occurred and were lengthy and resistant to treatment. Even after such a careful, informed and judicial clinical study as this, it is hard to assay the value of this newer form of anti-rheumatic therapy. It has its seeming triumphs and its possible disasters. We have no exact knowledge as to why it should do good or how it does it. I think it is fair to say that if it be carefully controlled, the opinion seems to be growing that gold therapy has a better chance to survive than either sulphur or vaccine therapy.

*Endocrine Products.* There is some suggestive evidence (to be presented later) that we may find in certain endocrine extracts and hormones very useful therapeutic agents for the alleviation of certain types of chronic rheumatism.

*Climate.* Holbrook's<sup>21</sup> study of the incidence of chronic rheumatism among the population of the high and dry Arizona Desert and of some of the western Indian tribes suggests that we must accept the fact that elevation and dryness and sun exert at least a strongly inhibiting influence upon the incidence of atrophic or rheumatoid arthritis.

*Physical Therapy.* This is perhaps the oldest of the rheumatic "cures." It remains a powerful arrow in the quiver of therapy. I am convinced that it should be planned and supervised and frequently checked, not by a physical therapy technician but by the captain of the patient's fate himself. Otherwise grievous sins may be committed in its name.

*Reconstructive Surgery.* There remains, and probably always will remain, a certain number of sufferers from chronic rheumatism the fires of whose disease seem to have burnt out leaving them crippled to the point of almost complete disability. I speak from experience when I say that we may rehabilitate to varying but quite worthwhile degrees these pathetic individuals and that we owe them such surgical reconstruction. Wilson and the writer<sup>40</sup> have tried to emphasize the importance of such attempts and to describe the conditions which must obtain to warrant the hope of success.

Before we leave the subject of the therapy of chronic rheumatism, may I say that although we possess no specific curative agent for either of the great types of unknown etiology, we are enthusiastic and not depressed by the results of treatment of the chronic rheumatic diseases by application of the knowledge we now possess. I believe from such statistics as Kalmeter has given us and from the follow-up of private practice, we may expect a certain number of cures, a certain number of remissions, a lesser number of exacerbations and an almost negligible number of patients who will not admit that our care has lightened their load.

**Social Approach to the Problem of Chronic Rheumatism.** The problem of chronic disease in general has become more serious as the percentage of life expectancy has risen and will apparently continue to rise for many years. The increase of chronic disease is greatest after the age of 45. Two other facts should prick our social and

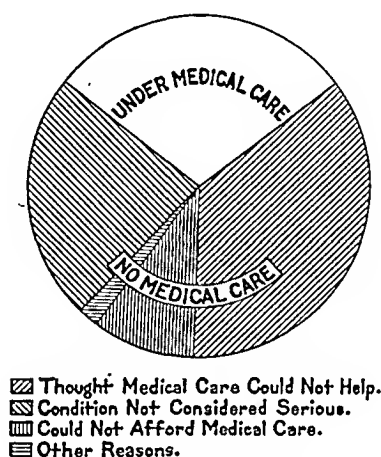


CHART 3.

medical consciences. The findings of the Massachusetts Survey<sup>4b</sup> revealed the incidence of chronic disease to be nearly twice as high among the poor as among the well-to-do. This fact is of serious social import. Medically, we should be chagrined, if not alarmed, to realize that four-fifths of the poor and one-half of the well-to-do who were suffering from chronic disease were not under the care of any physician. These findings are a challenge to social service and no less to the medical profession.

The first approach to this social problem would seem to be a change in the education of medical students. Unless they can be made more aware of the incidence of chronic disease and of the methods of approach and treatment we cannot expect to solve the social problem.

Our next social approach would seem to be the establishment of hospitals (not of almshouses) for the study and treatment of chronic

disease. We are of the opinion that the time is ripe for the establishment of separate departments in large general hospitals or of several large hospitals of this character, in many of the great cities, because of the notable recent increase in the number of outstanding physicians who have acquired an acute scientific and humanitarian interest in the chronic rheumatic diseases. These institutions will be expensive to erect, equip and conduct. If philanthropy fails, I believe municipal, state or even Federal financial help should be sought and can be cogently argued for on the grounds of economy alone, but only if there exist in a given community a sufficient number of highly trained physicians acutely interested in helping to solve the medical and social problems which the chronic rheumatic diseases present.

**The Look Ahead.** I shall attempt in closing to hazard a look into the future, an attempt always dangerous, but the obvious approach to the study of a disease is to proceed from the known to the unknown.

We know that "chronic rheumatism" includes not one but many diseases. We know that trauma, infection, chemical or metabolic disturbances can cause injury to the joints which present varied pathologic patterns. The picture will depend upon the nature of the injurious agent and upon the intensity and duration of its action. The pathologic pictures resulting from causes of known origin, however, are by no means always distinguishable from pathologic pictures the exact causes of which are unknown. This should not surprise us since we know that the tissues of the joints have the power of reacting in only a limited number of ways to various types of insult.

As clinicians we must be aware of the existence of the different types of chronic rheumatism. It is easy to assume that the sole cause of hypertrophic or degenerative joint disease is senescence plus gross or slight functional trauma. The blood may show only a mild anemia and yet the patient may improve both symptomatically and functionally under a therapy of vitamin B complex by mouth and by injections of liver extract.

A second group represents what for lack of a better name we may call arthralgia. My colleague, Dr. Hall,<sup>16</sup> has studied a series of 85 patients in whom for various reasons an artificial menopause had been produced and who had been free from articular or muscular disturbances before castration. Seventy-five per cent of these patients believed that they were suffering from arthritis, but the usual causes for arthritis could not be found. Sometimes joints and muscles were tender to pressure; sometimes joint motions were limited and painful; sometimes the blood sedimentation rate was elevated. They resembled patients with early atrophic or rheumatoid arthritis, complaining of morning stiffness and often of swelling of the joints. Indeed he was unable to make a definite diagnosis.

He decided to observe them carefully and administer estrogenic therapy. The results of treatment with the ovarian hormones were often quick and dramatic. The evidence suggested increased vulnerability of the muscles and joints.

Certain suggestive observations have been made on several younger women complaining of arthralgia who possessed low stamina, small breasts and whose menstrual flow was painful and scanty. He suspected an ovarian deficiency. One of these young women whose malady had been diagnosed as rheumatic fever has been followed now for 3 years and her symptoms are quite well controlled by this form of therapy. A married woman of 28 sought consultation during the fourth week of her third attack of what had been called infectious arthritis. Each attack had been preceded by an acute upper respiratory infection and in the two previous attacks she had been confined to her bed for 3 and 6 months. Examination showed slightly limited motion in both hips and knees and tenderness to pressure over both the knee and finger joints. No foci of infection could be found, the electrocardiogram was normal, and the sedimentation index was high, 1.0. Otherwise the physical examination was negative. The history revealed very scanty, painful, disabling menstruation which had led her to submit to an exploratory pelvic operation and a division of the pubic nerve. Under large doses of estrogenic substance she was free from symptoms in 2 weeks. What appears to happen when an infection strikes a person with ovarian gland deficiency may well happen when an infection occurs in a patient with a food deficiency, let us say of vitamin B. It is interesting that McCarrison,<sup>22</sup> writing years ago on food deficiency, expressed his opinion that such a sequence of events takes place.

In discussing hypertrophic arthritis or degenerative joint disease you may remember that we confessed to a little doubt in our minds as to whether in all cases senescence and wear and tear, important as they are, were always the *only* important etiologic factors. One more clinical case will illustrate why our minds are still open.

We have followed for 8 years a patient of over 50 years, seen first because of an almost crippling affection of the right hip joint, a typical *malum coxae senilis* or degenerative joint disease. The left hip also was very slightly involved. She has been coöperative in every way. She has worked assiduously on prescribed general and special exercises looking to the correction of faulty body mechanics and exercises for the affected leg in particular. Because of a suspected lack she has been given considerable quantities of estrogenic material. The joint motion has increased in all ranges, especially in internal rotation which in our experience rarely returns when lost. Muscle spasm has disappeared.

I refer again to the dramatic and sometimes complete remission of the symptoms of atrophic or rheumatoid arthritis associated with

severe jaundice and pregnancy. If we can find the substance produced in the body which is responsible for these remissions we might hope to approach an important etiologic agent. No endocrine disturbance has yet been proved to be the sole cause of any type of chronic rheumatism. The rationale of an endocrine lead, however, is suggested by the following considerations:

We know that pregnancy may cause true remission of atrophic or rheumatoid arthritis. If we could reproduce the biochemical conditions of pregnancy or if we should find that patients who suffer from this disease frequently lack some substance present in the pregnant woman, we might be able to arrest the disease and approach a specific therapy.

From our present knowledge the major hormone increase in pregnancy is the estrogenic hormone, for during pregnancy the placenta manufactures huge quantities of the hormone. The absence of this hormone may explain the frequency of joint disturbances at the menopause, said to represent 24% in a study of 1000 women.<sup>23</sup> Its absence may also explain why women are prone to develop arthritis after miscarriage and after pregnancy and lactation.

It must be remembered that at least two things may happen after castration: *a*, removal of ovarian hormones from the body; and, *b*, resulting overactivity of the anterior pituitary gland which floods the body with pituitary hormones. Young<sup>41</sup> and others have shown that overactivity of the pituitary hormones may damage the pancreas and produce diabetes. We know that it may damage the gonads as in acromegaly. Do these facts not justify us in wondering whether excess of anterior pituitary excretion may not damage the joint structures also? Irradiation of the pituitary by Roentgen ray seems to relieve disturbances associated with the true menopause and the administration of estrogenic substance has the same effect.

It is possible that the administration of estrogenic substance may prove to be an important form of replacement therapy in arthritis and that it may put a brake on anterior pituitary excretion.

There are two pieces of suggestive evidence in this connection. Putnam<sup>31</sup> and his associates, in producing in dogs experimental acromegaly in 1928 by the administration of pituitary substance, found at necropsy not only enlarged bones but osteophytes on their prominences and on the patella and what may be still more suggestive, separate flakes of bone lying in the anterior ligament of the spine. Putnam and Davidoff,<sup>30</sup> in later work on acromegaly in 1936, report finding osteophytes indistinguishable from those seen in hypertrophic arthritis or degenerative joint disease extending into tendons and ligaments and sometimes fastening several vertebrae together.

The other piece of suggestive evidence has been furnished by the

work of the two Silberbergs, M. and R.<sup>35</sup> I quote from their article, "A Comparison of the Effects of Anterior Pituitary on Skeletal Tissues of Young and Adult Guinea Pigs": "The severe arthropathic changes which were produced by the anterior pituitary hormone in old (mature) animals are comparable to those taking place in 'arthritis deformans' in man." By the term "arthritis deformans" I fancy they are referring to hypertrophic arthritis or degenerative joint disease.

I have no conviction that either the exact etiology or the rational treatment of atrophic or rheumatoid arthritis or of hypertrophic or degenerative joint disease has been found. These findings in experimental animals and a small amount of clinical work merely suggest that more intensive and extensive clinical and laboratory research along these lines should be encouraged.

I desire to acknowledge that in the preparation of this paper I have received generous help from my friend and medical colleague, Dr. Francis C. Hall. He is a much better rheumatologist than I, because as an internist his breadth of view is wider.

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## "TARGET CELL" ANEMIA.

### ANERYTHROBLASTIC TYPE OF COOLEY'S ERYTHROBLASTIC ANEMIA.\*

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INVESTIGATION of the case of an Italian youth of 20 who presented anemia and splenomegaly revealed a peculiar abnormality of the erythrocytes and a generalized disturbance of the bones. Many of the red cells presented a "bull's eye" or "target" appearance; the bones showed thickening and an unusual "honeycomb" appearance. In addition a large tumor originating from one of the ribs and involving the right lung was discovered. Since an outstanding abnormality was the presence of large numbers of peculiar erythrocytes designated as "target cells" by Barrett,<sup>3</sup> the name "target cell anemia" was adopted for this previously undescribed condition. Although no nucleated red cells were present in the peripheral blood, the possibility that the condition might be a *forme fruste* or an anerythroblastic type of Cooley's anemia was considered. The report which follows is based upon a preliminary study of the case.†

**Case Report.** Joseph C., aged 20, of Italian parentage, was referred by Dr. I. M. Blumerfield on May 5, 1939. He had no complaints. In the course of a visit to another member of the family, the doctor had noticed the boy's yellowish pallor. On examination in March, 1939, splenomegaly was discovered and blood studies revealed a hypochromic anemia (Hgb. 43%, R.B.C. 2.45 million). After 3 weeks of treatment with ferrous sulphate (12 gr. daily) the hemoglobin rose to 55% and the erythrocyte count to 3.39 million. Because of the persistent splenomegaly, further study was considered desirable.

The patient was born in Boston of Italian (Sicilian) parentage. His father and mother were alive and well. One sister and 3 brothers were well; 1 sister was "queer" and "dropped things;" 1 brother was a mental defective. Examination of the family revealed no icterus, anemia, or other hematologic abnormalities except in the well sister, who had a slight hypo-

\* Aided by a grant from the Charlton Fund of Tufts College Medical School.

† An abstract of this article appeared in the Bull. New England Med. Center, 2, 101, 1940.



chromic anemia and 3.4% of target cells (see below). The "queer" sister was found to have athetoid movements of the hands, arms, and legs, and the diagnosis of Wilson's disease (lenticular degeneration) was made by a neurologist. No evidences of anemia, hepatic insufficiency, or of bone disturbance were present.

In 1925, at the age of 5, the patient had been studied at another hospital, where he had been admitted because of fever. Full records of this hospital admission were fortunately available. Physical examination disclosed marked pallor, large injected tonsils, a somewhat enlarged heart with a systolic murmur diffusely heard over the precordium, and an enlarged spleen which was felt 3 to 4 cm. below the left costal margin. The hematologic findings were as follows: Hgb. 42% (Sahli), R.B.C. 2.60 million, W.B.C. 10,200, platelets 216,000 (direct method), reticulocytes 7%; sodium chloride fragility test: hemolysis began at 0.475—complete at 0.275; differential count: P. 54, L. 39, M. 2, B. 4, E. 1; the red cells showed slight to moderate achromia, anisocytosis and poikilocytosis; no nucleated red cells

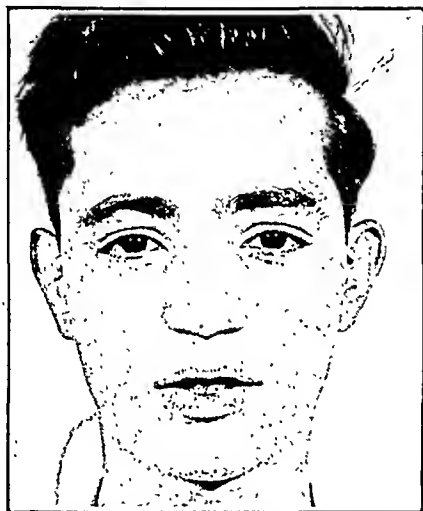


FIG. 1.—J. C., an Italian boy, aged 20, with "target cell anemia"—anerythroblastic type of Cooley's erythroblastic anemia. There is no definite Mongoloid appearance of the face.

were observed. Other laboratory findings, including blood cultures, were negative. While in the hospital, there was improvement in the anemia. A definite diagnosis was not made after 5 weeks of study, although the possibility of Hanot's cirrhosis was considered. Roentgen rays of the bones were not taken. The patient was discharged (against advice) with the diagnosis of acute pharyngitis and ? Hanot's cirrhosis.

Since then, except for a tendency to underweight, the patient had felt well. The family had noticed yellowish pallor for about 2 years. In the past year he had gained 17 pounds in weight (from 125 to 142 pounds). After graduation from high school, he had performed occasional clerical jobs, but was usually unemployed. Except for smoking a few cigarettes daily, he had no unusual habits. He was extremely uncoöperative regarding investigation, so that repeated studies were difficult to obtain. He refused hospitalization.

*Physical examination* in May, 1939, revealed a well-developed, rather tall, somewhat pale, slightly icteric young man. He looked typically



FIG. 2.—Stained blood smear ( $\times 560$ ). Note the great diversity in size and shape of the red cells and the large number of "target cells."

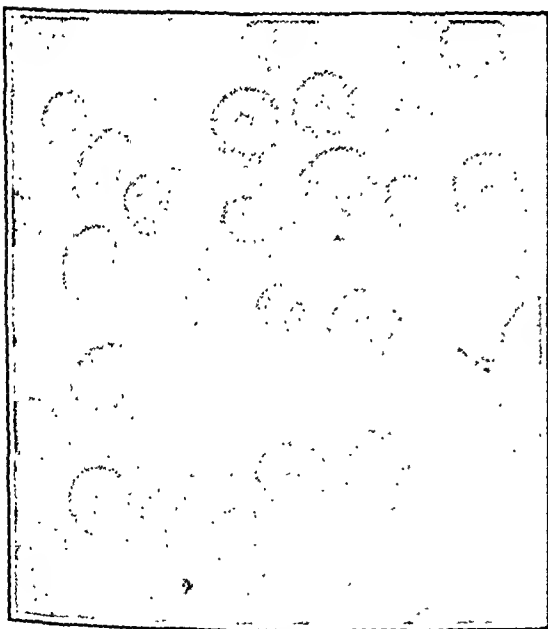


FIG. 3

FIG. 3.—Stained blood smear ( $\times 1000$ ). Typical "bull's eye" or "target cell" forms are seen, together with some having "bridges" between the "eye" and the periphery of the erythrocyte.



FIG. 4

FIG. 4.—Fresh, unstained, unmodified preparation of blood. Note the very thin cells seen on end, the tendency of these cells to buckle and to form cup-shapes, and so on, and the impaired rouleaux formation due to diversity in erythrocytic configuration.

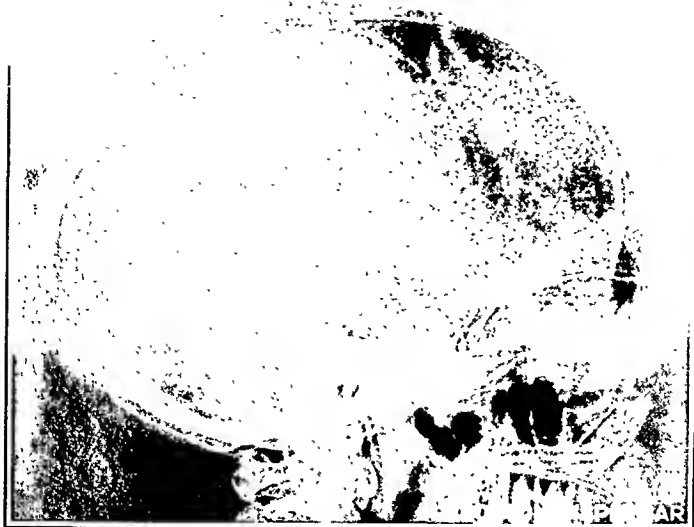


FIG. 6



FIG. 7

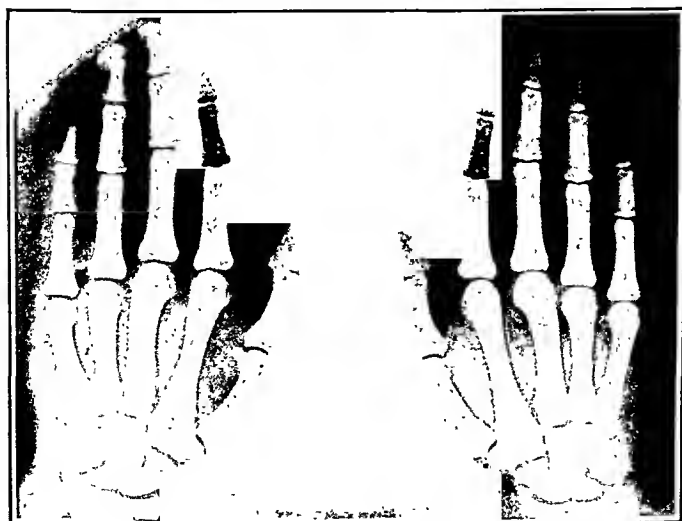


FIG. 8

"Italian" and did not then present Mongoloid features. However, in December, 1939, when anemia was more pronounced, he presented a well-marked Mongoloid appearance, perhaps due to the greater icterus and pallor at that time. The heart was not enlarged; a loud, blowing systolic murmur was present at the apex and along the left border of the sternum; no presystolic or diastolic murmurs were heard. The liver dullness was not increased and the liver edge was not palpable. The spleen was readily felt 3 to 4 finger breadths below the left costal margin. There were no "spider" telangiectases. The remainder of the examination was negative.

TABLE 1.—JOSEPH C. LABORATORY DATA.

	March, 1939.	FeSO <sub>4</sub> , 1.0 gm./d., March-May.	May, 1939.	No treat- ment.	December, 1939.
Hgb. (Evelyn) 100% 15.6 gm. . . . .	43	..	67	..	50
Erythrocytes . . . . .	2.45	..	4.28	..	3.12
Leukocytes . . . . .	..	..	6100	..	5200
Platelets . . . . .	..	..	560,000	..	1,051,000
Reticulocytes (%) . . . . .	..	..	0.9	..	5.1
Target cells (%) . . . . .	..	..	26	..	32
Hematocrit (%) . . . . .	..	..	35	..	25
M.C.V.* (cu. micra) . . . . .	..	..	81	..	80
M.C.D.* (micra) . . . . .	..	..	7.6	..	7.4
M.C.T.* (micra) . . . . .	..	..	1.8	..	1.85
M.C.H.* (micro-microgm.) . . . . .	..	..	24.5	..	25
M.C.H.C.* (%) . . . . .	..	..	30	..	31
Fragility (saline) . . . . .	..	..	.42-.04	..	.44-.04
Bilirubin (mg.) . . . . .	..	..	1.9-2.4	..	2.4
Calcium (mg.) . . . . .	..	..	..	..	10.7
Phosphorus (mg.) . . . . .	..	..	..	..	3.8-4.5
Phosphatase (Bodansky units) . . . . .	..	..	..	..	2.0
Cholesterol: Total . . . . .	..	..	124	..	74
Esters . . . . .	..	..	..	..	54

\* These initials indicate mean corpuscular volume, diameter, thickness, hemoglobin and hemoglobin concentration, respectively.

The laboratory data were as follows: *Urine*: no albumin, sugar, or bilirubin; the urobilinogen content was 1 to 20 (Wallace and Diamond). *Stool*: dark brown in color; the daily fecal urobilinogen output (Watson method) was 890 mg. *Blood chemistry*: icterus index 20, 22.5; bilirubin (indirect type) 1.9, 2.4 mg. per 100 cc.; serum calcium 10.7; phosphorus 3.8, 4.5; alkaline phosphatase 2 Bodansky units, total cholesterol 75 and 125 mg., cholesterol esters 54 mg. The bromsulphalein liver function test showed 6% retention of the dye at the end of 30 minutes (normal). Negative Kahn and Hinton tests of the blood serum. *Hematology*: (see Table 1)

## LEGENDS FOR FIGS. 6, 7 AND 8.

FIG. 6.—Roentgen film of skull. Note the thickening of the diploë and the diffuse "honeycomb" appearance.

FIG. 7.—Roentgen ray of the chest demonstrated a large tumor composed of bone and soft tissue, probably hyperplastic bone-marrow, together with partial destruction of the 6th rib.

FIG. 8.—Roentgen rays of the hands showed striking osteoporotic changes, particularly of the metacarpal bones. Similar changes were demonstrated in all the other bones.

this showed a hypochromic type of anemia with some tendency to leukopenia and granulocytopenia. In March, 1939, when the anemia was slight, the mean corpuscular volume was 81 cu. micra, the mean cell diameter 7.6 micra, and the mean cell thickness 1.8 micra (normal approximately 2 micra in our series). The data for mean corpuscular volume and cell thickness were essentially unchanged when the anemia was more pronounced in December, 1939. The fragility test showed greatly *increased resistance* to hypotonic salt solutions: hemolysis commenced at 0.42 to 0.40% and was incomplete at 0.04% (normal controls: beginning hemolysis 0.44 to 0.46—complete hemolysis 0.24 to 0.22). In 0.3% solution of sodium chloride, approximately 33% of the cells were "resistant" (*i. e.*, unhemolyzed). The outstanding feature of the blood smear was the presence of large numbers of typical target cells as described by Barrett and as confirmed by us in such conditions as severe hepatic disease, following splenectomy, and in sickle-cell anemia. The percentage of typical target cells varied from 26 to 33% of the total red cells.

*Target Cells.* The typical target cell in stained preparations is shaped like a bull's eye, with a peripheral ring of hemoglobin separated by a clear unstained zone from a dense central "eye." This characteristic appearance of the target cell is modified in other cells, in which a "bridge" of hemoglobin is seen between the peripheral and central masses of hemoglobin. Various gradations between the typical target cell and those with "bridges" may be noted.

TABLE 2.—C. FAMILY. HEMATOLOGIC DATA.

	Anna (mother).	Orazio (father).	George.	Tony.	Lucy.	Mary.
Hemoglobin . . . . .	..	..	..	..	87	68
Erythrocytes . . . . .	..	..	..	..	4.36	4.72
Leukocytes . . . . .	..	..	..	..	5700	6600
Reticulocytes (%) . . . .	0.5	0.5	0.2	0.3	0.2	2.4
Target cells (%) . . . . .	0.0	Rare	0.0	0.0	0.0	3.4
Hematoerit (%) . . . . .	..	..	..	..	42	35
M.C.V. (cu. micra) . . . .	..	..	..	..	96	74
Fragility (saline) . . . .	..	..	..	..	.42-.24	.42-.16
Bilirubin (mg. per 100 cc.)	..	..	..	..	0.5	

The differing appearances of the target cells may be explained, as Barrett points out, by assuming for the cell a central thickening, like that of a squat collar-button. When viewed on end, this cell would have the appearance of a Mexican hat, as Haden has suggested. Viewed from above at different levels these cells present either a bull's eye appearance or show bridged forms.

Differential Price-Jones diameter counts in our case revealed that the target cells were larger than the average red cell in the same preparations. Whereas the average red cell diameter for all the red cells was 7.6 micra, that of the target cells was 8.6 micra. This finding is quite in contrast with that of Barrett in a case of obstructive jaundice in which he found that the diameter of target cells was smaller (7.6 micra) than that of the average red cell (8.04). This difference can probably be explained on differences in the two types of cases since the case described by Barrett was probably one of macrocytic anemia (of hepatic disease), whereas our case presented a diminished mean corpuscular volume.

In fresh preparations, the cells formed rather poor rouleaux, composed of cells which varied greatly in their configuration. Isolated cells appeared

definitely thinner and more flexible than normal, changing shape readily. Cells viewed on end not infrequently presented a bulging of the central mass of hemoglobin apparently due to buckling of the unusually thin cell. Cup-shaped forms were commonly seen. When viewed from above these cells usually presented a very distinct circular appearance with at times a suggestion of bull's eye appearance. This could be accentuated by placing the preparation somewhat out of focus.

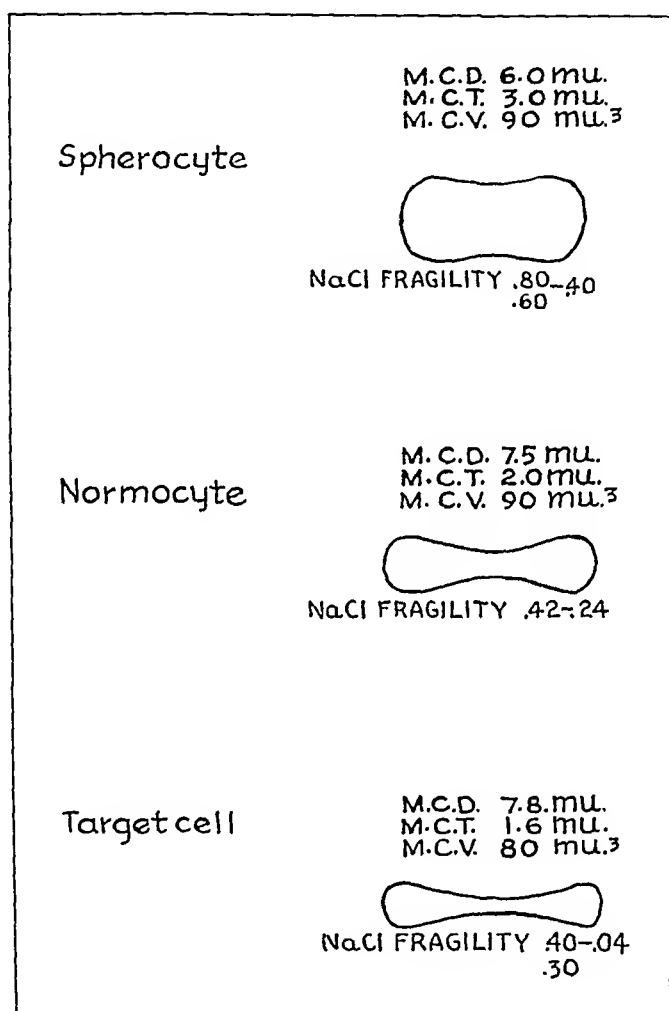


FIG. 5.—Representation of some of the physical differences between the normal red cell, the thick spherocyte, and the thin target cell. The thinner the red cell, the more resistant is it to hypotonic hemolysis.

*Roentgen Ray Findings.* The unusual nature of the Roentgen ray findings was not at first suspected but was fortunately discovered when films of the esophagus for varices were requested. The latter were negative. Films of the chest showed a large tumor of bony structure, irregularly trabeculated, oval in shape, measuring 9 by 8 by 8 cm. and occupying the medial and posterior portion of the right upper lung field. In the region of this mass, the sixth rib posteriorly was destroyed, particularly in its

medial aspect, to about 6 cm. from its vertebral articulation. All the ribs, the clavicles, the scapulæ, and the humeri showed numerous irregular areas of increased radiance with coarse irregular trabeculations. Roentgen rays of the skull showed great thickening of the inner and outer tables with the same honeycomb appearance. All the facial bones, including the jaw, were involved. The bones of the pelvis, the thighs, the hands, and feet were similarly affected in greater or less degree, the metacarpal bones showing the most striking osteoporotic changes. Flat plates of the abdomen showed marked enlargement of the spleen, the lower border extending below the level of the crest of the ilium, and from the lateral aspect of the abdomen to almost the left border of the spine.

*Bone-marrow Biopsy.* Sternal puncture revealed one of the most cellular marrows ever obtained in our experience. The ratio of nucleated red cells to white cells was 4 to 1 (normal in puncture preparations about 0.5 to 1). Differential count of 500 cells showed: erythrogonies 6.4%, normoblasts A 9.6%, normoblasts B 32%, normoblasts C 35%, myeloblasts 1.6%, myelocytes 5.4%, metamyelocytes 7.6%, mature polymorphs. 2.4%, histiocytes 0.6%. The erythroblastic cells contained in general very small amounts of cytoplasm.

**Comment.** 1. *Target Cells.* Although the only extensive studies of this unusual type of red blood corpuscle have been made by Barrett,<sup>3</sup> they were first described as a special type of erythrocyte by Haden and Evans.<sup>12</sup> The latter authors refer to them as "dimpled corpuscles" and liken their form to that of a Mexican hat. They state: "One occasionally sees a few cells of this shape in other anemias, but they are never present in any significant number except in sickle cell anemia." This statement has been criticized by Barrett, with whom we can agree that the target cell is found in significant numbers in some cases of obstructive jaundice and severe hepatitis, in some cases of hypochromic anemia, and following splenectomy. In addition, we have (for the first time) demonstrated substantial and at times large numbers of these cells in Cooley's erythroblastic anemia.

Our studies\* of the target cell confirm those of Barrett. The cell is abnormally thin, tends to "buckle" and to present in stained preparations a bull's eye appearance. In contradistinction to the thick spherocyte, the target cells are unusually resistant to hypotonic solutions of sodium chloride. When these cells are present in any significant number (over 4%) they result in a lengthening of the fragility span, with complete hemolysis occurring between 0.16 and 0.02%, depending upon the number of these cells present. In the case described, hemolysis was incomplete at a concentration of sodium chloride of 0.04%. Examination of the centrifuged red cells from concentrations of sodium chloride below 0.30%, following resuspension in the patient's own (heparinized) plasma demonstrated the high concentration of target cells. When the red cells were suspended in varying concentrations of hypotonic solutions of

\* To be published.

sodium chloride and the hematocrits determined, the following figures were obtained:

Concentration of NaCl solution.	Hematocrit (%)	Mean corpuscular volume (cu. micra).
Unmodified (in isotonic oxalate) solution	25	80
.80	30	96
.72	32	102
.60	34	109
.40	40	128
.30	45	144

Traces of hemolysis were present in the 0.40 and 0.30 concentrations of sodium chloride solution. Before moderate hemolysis occurred (below the concentration of 0.30%), the cells had almost doubled in volume, thus indicating their unusual capacity for taking up water before hemolysis resulted (Haden<sup>11</sup>).

The target cell may be said to be the antithesis of the spherocyte. Haden,<sup>11</sup> and Castle and Daland<sup>7</sup> concluded that the thick cells of hemolytic jaundice were unusually fragile to hypotonic salt solutions because less swelling was required to rupture an almost spherical cell than one with a discoidal form. As the result of experimental studies on hemolytic anemia, Dameshek and Schwartz<sup>10</sup> concluded that the spherocyte was a red cell which had been damaged by a hemolytic agent with consequent loss of the normal biconcave shape. A completely spherical cell, representing the greatest damage by hemolysin, bursts even in solutions of salt only slightly hypotonic (0.84 to 0.76). At the other extreme, the cell which is unusually thin can absorb a large quantity of fluid before it finally reaches the bursting stage, or complete hemolysis. The abnormally thin target cell is thus able to withstand hemolysis at exceedingly low concentrations of sodium chloride.

2. "*Target Cell Anemia*" and Related States. The criticism may be made that there is insufficient justification for the use of the designation of "target cell anemia" in the case here presented. It is conceded that this designation tends to focus attention on an abnormality which is perhaps not fundamental, but that other abnormalities (such as those relating to the spleen or the marrow) may be of greater importance. However, the same criticism may be made for the nomenclature in use for most states associated with anemia, *i. e.*, pernicious anemia, hypochromic anemia, and aplastic anemia. Sufficient precedent for this type of designation exists, moreover, in the conditions known as sickle cell anemia, erythroblastic anemia, erythroblastosis of the newborn and so on. Until it is possible to classify all types of anemia on an etiologic basis, the retention of such graphic terms is probably justifiable, providing one realizes that the designation used represents only one feature of some more fundamental abnormality.

Target cell anemia may be closely related to or indeed even a phase of the condition known as erythroblastic or Mediterranean



anemia. Certain similarities are evident: the racial factor (Italian in our case); the somewhat Mongoloid appearance; the hypochromic anemia with splenomegaly; the increased resistance of the red cells to hypotonic salt solutions; the bilirubinemia; and the well-marked and generalized bone changes with great thickening of the skull. Because of these similarities, we investigated the blood picture of a few cases of Cooley's anemia.\* In all of these, target cells in variable number were found, very large numbers being present in 1 splenectomized case. Lehdorff,<sup>14</sup> in his monographic article on Cooley's anemia, describes these cells without, however, further designating them; excellent illustrations of the various types of abnormal erythrocytes are given in the colored plate of his article.

Certain differences may be pointed out between our case and those of erythroblastic anemia:<sup>4,8a,9</sup> 1, the boy was fundamentally in fair health at the age of 20 (this is exceptional in Cooley's anemia); 2, he had a hypochromic anemia which responded well to the administration of iron; this does not ordinarily occur in Cooley's anemia; 3, no nucleated red cells were found in the blood smears either in 1925 at the age of 5 or in 1939 at the age of 20; the term "erythroblastic anemia" indicates that the outstanding feature is the presence of numbers of nucleated red cells; 4, the Roentgen ray appearances of the bones differed slightly (but not fundamentally) from those in Cooley's anemia, *i. e.*, there was no "hair-brush" effect in the Roentgen rays of the skull, and according to two roentgenologists, the appearance of the bony trabeculations differed somewhat from that of Cooley's anemia.† The finding of a bony tumor encroaching on the lung is a unique observation.

These differences may be merely superficial. The boy might have had erythroblastic anemia as an infant and might have quickly "outgrown" it. (No nucleated red cells were, however, present at the age of 5.) The lack of nucleated red cells in the blood might be indicative of either complete recovery, a more or less "spent" state, or of a latent or *forme fruste* condition. The exceedingly hyperplastic marrow picture might have the same relationship to an "anerythroblastic" picture as the marrow crowded with myeloblasts has to an "aleukemic" blood picture with leukopenia and absence of primitive cells. The slight differences in the bone changes from the typical cases of early childhood might be on the basis of growth and gradual change in the bone picture.

The target cell and its relation to Cooley's erythroblastic anemia may be looked upon from another, and perhaps more fundamental aspect. That is, the basic abnormality in Cooley's anemia might not be the nucleated red blood cell, which indeed is non-specific since erythroblastosis occurs in many conditions, but the target cell.

\* We are indebted to Drs. Louis K. Diamond of the Children's Hospital, and James M. Baty of the Boston Floating Hospital for their coöperation.

† We are indebted to Drs. Alice Ettinger, Pratt Diagnostic Hospital; Samuel A. Robins, Beth Israel Hospital; George M. Wyatt, Children's Hospital; E. C. Vogt and Felix Fleischnier for their examinations of the roentgenograms and their interpretations.

This cell, which is unusually resistant to hypotonic solutions of NaCl, might be the result of an hereditary defect of red cell production in the bone-marrow, with or without relationship to a splenic abnormality. The extremely hyperplastic bone-marrow, which results in the well-known osteoporotic changes, is ordinarily reflected by erythroblastosis in the peripheral blood, but it is conceivable, as in the case here presented, that in certain so-called latent cases, target cells and not erythroblasts may dominate the blood picture.

Caffey,<sup>5</sup> in his review of the roentgenologic changes in Cooley's anemia, observes that certain cases show the long bone changes yet lack the characteristic thickening and linear striations of the skull. He believes that certain mild cases probably reach adulthood and might even transmit the disease.\* This speculation is placed on firm foundation by the work of Caminopetros<sup>6</sup> who demonstrated that certain non-affected members of families with cases of the disease showed an increased resistance of the red cells to hypotonic solutions of salt. This leads to the definite possibility that the target cell is the inherited factor responsible for the disease known, in its full-blown state, as Cooley's erythroblastic anemia.

The coëxistence of the resistant target cells with a hemolytic tendency as manifested by "indirect" bilirubinemia and an increased output of urobilinogen in the feces may at first glance appear somewhat paradoxical. This feature, together with the lack of response to splenectomy in both Cooley's and sickle cell anemia are quite in contrast with those of the "typical" hemolytic anemias in which spherocytosis, increased fragility and dramatic response to splenectomy are common, and may indicate possible relationships between the former condition. Although the red cells of erythroblastic anemia, sickle cell anemia, and target cell anemia are *more* resistant to solutions of hypotonic sodium chloride *in vitro*, it is possible that they may be *less* resistant to breakdown *in vivo*, with resultant evidences of increased hemolysis.

Bone changes are common in Cooley's anemia, but similar changes are occasionally found in sickle cell anemia and (to less extent) in congenital hemolytic jaundice.<sup>8b</sup> They probably represent a greatly expanded marrow cavity in the presence of extreme hyperplasia. The bone changes in our case are probably explicable on the same basis. The tumor arising from one of the ribs, composed in part of relatively soft-appearing tissue and in part of bone, probably represents a large mass of ectopic bone-marrow which has resulted from great expansion due to unusual hyperplasia.

**Summary.** In an Italian youth with hypochromic anemia, splenomegaly, and a hemolytic type of icterus, unusual changes were discovered in the red blood cells and the bones. About a third of the red cells presented the appearance of "targets" or "bull's eyes;" these cells were unusually resistant to hypotonic solutions of sodium chloride. No nucleated red cells were present. Generalized osteo-

\* Eight cases have been reported in individuals over the age of 14.<sup>1,2,4,8c,12,13,16</sup>

porotic changes with great thickening of the skull were present; in addition a bony tumor arising from a rib encroached on the right upper lung. Target cells have been described in sickle cell anemia, cirrhosis of the liver, chronic hypochromic anemia after splenectomy, and in other conditions. The present studies have shown that they are also common in Cooley's erythroblastic anemia.

The condition of "target cell anemia" as described in this paper may be a *forme fruste*, an anerythroblastic type of Cooley's erythroblastic anemia or a closely related condition. The possibility is broached that Cooley's anemia, sickle cell anemia, and target cell anemia are related conditions with target cells and increased saline resistance as common denominators. In Cooley's anemia, the target cell is probably a more fundamental abnormality than the erythroblast, and may represent the basic hereditary defect. In these atypical hemolytic states, a lack of response to splenectomy further differentiates them from most cases of congenital and acquired hemolytic icterus.\*

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### ANEMIA AND WATER RETENTION.

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EDEMA is of common occurrence in anemic patients. Addison in 1855<sup>1</sup> describing the anemia which now bears his name, wrote

\* The very interesting paper of Wintrobe, Matthews, Pollack, and Dobyns (Jour. Am. Med. Assn., 114, 1530, 1940) appeared while the present article was in press. The identical disorder is described as "A Familial Hemopoietic Disorder in Italian Adolescents and Adults resembling Mediterranean Disease (Thalheimer)". The authors of this paper, which is based on a more extensive material, bring out substantially, the same findings as our own.

"some slight edema is probably perceived about the ankles." This edema, at one time ascribed to cardiac weakness, and more recently attributed to a concomitant lowering of the plasma protein level, has been shown to occur independently of the latter.<sup>6,7,9</sup> Peters and Eisenman<sup>9</sup> suggest that "some characteristic of the condition of anemia itself tends to facilitate the appearance of edema." Schade, Claussen and Birner<sup>10</sup> found that, at a given perfusion pressure, whole blood tended to withdraw more fluid from the surrounding medium than did its own serum. These observations, however, as pointed out by Peters and Eisenman<sup>9</sup> were made with biologically inert collodion membranes, not subject to nutritive disturbances which might alter capillary permeability.

The presence or absence of edema, and its magnitude, when present, is a matter of clinical judgment. There is no way that the amount of edema present at any one observation can be quantitatively measured in any but the most crude manner. It is a well-known fact that patients with heart disease who have fairly extensive dependent edema at night may awaken in the morning with little or no evident edema, but without change in body weight, indicating that a redistribution of the edema fluid has concealed its presence. Similarly, patients with "nephrotic" edema may shift this fluid during the day so that eyelids almost closed with edema on awakening are normal in the evening. It has further been shown that some individuals may retain as much as 5 or more kilograms of water without showing manifest edema whereas others will reveal as little as one kilogram of retained fluid with pitting edema.

In a previous study of water retention and edema formation in pregnancy<sup>11</sup> it was found that one could measure the "tendency to edema" by observing the changes in body weight which occur within a relatively short period of time following the administration or withdrawal of sodium salts. In pregnant women it was found that, in the absence of anemia, the percentage increase in body weight following the administration of sodium salts could be correlated in linear fashion with the colloid osmotic pressure of the plasma proteins. It was therefore decided to make similar observations on non-pregnant patients with varying degrees of anemia.

**Methods.** Thirty-two observations made on 26 patients will be discussed first (Table 1). Nine patients had pernicious anemia in mild relapse while under inadequate treatment. Eight patients had hypochromic anemia, 2 associated with chronic blood loss due to carcinoma of the stomach, 1 associated with the Plummer-Vinson syndrome, 1 with metrorrhagia, 1 with pellagra and 3 due to chronic blood loss from hemorrhoids. Six patients had anemia secondary to acute blood loss, in 1 case epistaxis, and in the remaining 5 instances due to peptic ulcer. These 14 patients were not studied until at least 1 week after bleeding had ceased. There were also studied 3 patients without anemia, 2 of whom were convalescent from acute respiratory infections, and 1 with peptic ulcer.

All patients were ambulatory on the hospital ward. They were permitted fluids *ad libitum* and partook of ward diets. They were weighed at the same time each morning. Blood for hemoglobin and plasma protein determina-

tions was withdrawn without stasis from an antecubital vein after the patients had been at rest for twenty minutes or more. Venous pressure determinations were made on 11 patients by the method of Moritz and von Tabora.<sup>8</sup> Plasma protein values were determined by a micro-modification of Howe's technique.<sup>5</sup> The colloid osmotic pressure was calculated from the values for plasma albumin and globulin by the use of the nomogram of Wells, Youmans and Miller.<sup>13</sup> The patients were observed during a preliminary period of 3 or 4 days until their weights were stabilized. Then each one received daily for 10 days in divided doses, either 23 gm. of sodium bicarbonate or (in 2 cases only) 16 gm. of sodium chloride, containing the same amount of sodium as the larger dose of bicarbonate.

**Results.** The venous pressure, determined on 11 patients, was 3.0, 3.5, 4.5, 5.0, 6.0, 6.0, 7.5, 7.5, 8.0, 10.0, and 10.5 cm. of water, all of which are within the normal range.

The hemoglobin determinations varied from 30 to 94% of 15.6 gm. per 100 cc. (Table 1). The calculated colloid osmotic pressure of the plasma proteins varied from 63 to 98% of 300 mm. of water. These values, 15.6 gm. per 100 cc. for hemoglobin and 300 mm. of water for osmotic pressure, have been considered normal in this clinic. The lack of correlation between hemoglobin and osmotic pressure is apparent from Chart 1. The coefficient of correlation is 0.3786 with  $P = 0.05$ .\* The 2 patients who had both low plasma protein osmotic pressures and low hemoglobin values were suffering from carcinoma of the stomach with cachexia and pellagra, respectively. If these 2 are eliminated the coefficient of correlation drops to 0.2391 with  $P = > 0.1$ , an entire absence of significant correlation.

The maximum amount of water retained within a period of 10 days following the administration of sodium as measured by the weight gains varied from 0.8 to 10.8% of original body weight (Table 1). This maximum gain generally occurred by the sixth or seventh day after sodium administration was commenced. In many instances slight to moderate spontaneous diuresis occurred subsequently while sodium administration was continued as has been noted before.<sup>11</sup> In 12 of the 32 observations pitting edema was present at the time of the maximum water retention. In the patient who gained 10.8% of his original body weight this extended as high as the abdominal wall and râles were heard in both lower lungs. Following the withdrawal of sodium the râles and the edema disappeared.

The percentage of weight gain has been plotted against the plasma protein osmotic pressure in Chart 2. Slight if any correlation is apparent. The coefficient of correlation is 0.4990 with  $P = 0.01$ . In contrast to this the correlation between the weight gain and the hemoglobin is quite apparent in Chart 3. The coefficient of correlation is 0.7780 with  $P = 0.01$ , a highly significant correlation.

Since, in non-anemic patients there is a good correlation between weight gain and plasma protein osmotic pressure, an endeavor was made to correlate the weight gains in these patients with anemia with both plasma protein osmotic pressure and hemoglobin level.

\* Probability coefficient.

TABLE 1.—BLOOD LEVELS, PLASMA PROTEIN VALUES AND WEIGHT GAINS IN 32 OBSERVATIONS MADE ON 26 PATIENTS RECEIVING SODIUM SALTS.

Case No.	Sex.	Age.	R.B.C. (millions per c.mm.)	Hg. (% of 15.6 gm. per 100 cc.).	Total protein (gm. per 100 cc.).	Plasma albumin (gm. per 100 cc.).	Calculated colloid osmotic pressure (mm. H <sub>2</sub> O).	Weight gain in % of original body weight.	Day of maximum weight gain.	Manifest edema.	Diagnoses.
1	M	80	3.51	30	6.0	3.0	235	10.8	10	+	Hypochromic anemia due to chronic blood loss from carcinoma of stomach.
2	M	72	2.31	31	5.0	2.7	188	7.6	3	+	Hypochromic anemia due to chronic blood loss from carcinoma of stomach.
3	M	54	2.35	35	5.0	2.9	192	6.4	3	+	Hypochromic anemia; chronic alcoholism; pellagra.
4	M	53	1.65	37	5.6	3.8	245	4.6	9	0	Pericious anemia.
5	F	76	3.10	38	6.1	3.8	268	9.0	8	+	Hypochromic anemia due to metrorrhagia.
6	M	71	3.73	45	5.7	3.6	243	5.2	9	+	Hypochromic anemia due to chronic blood loss from carcinoma of stomach.
7	F	50	4.03	45	6.5	3.8	287	3.1	9	0	Hypochromic anemia from bleeding hemorrhoids.
8	F	45	3.70	46	6.6	3.8	290	4.1	8	+	Hypochromic anemia from bleeding hemorrhoids.
9	F	49	3.78	48	5.7	3.0	222	6.0	6	+	Anemia from severe epistaxis; hypertension.
10	M	58	3.80	49	5.9	3.3	242	5.5	10	+	Anemia of acute blood loss due to peptic ulcer.
11	F	58	2.45	54	5.6	3.6	230	3.9	5	0	Hypochromic anemia due to bleeding hemorrhoids and malnutrition.
12	F	56	4.60	55	5.5	3.3	225	7.7	9	+	Idiopathic hypochromic anemia with Plummer-Vinson syndrome.
13	M	59	3.94	55	5.8	3.6	250	3.4	6	0	Anemia of acute blood loss due to peptic ulcer.
14	F	53	3.43	58	5.6	3.5	240	4.5	5	+	Anemia of acute blood loss due to peptic ulcer; hypertension.
15	F	50	3.01	59	6.2	3.7	268	4.0	9	0	Anemia of acute blood loss due to peptic ulcer.
16	M	36	3.19	59	5.2	3.5	230	3.4	9	0	Anemia of acute blood loss due to peptic ulcer.
17	M	31	3.58	60	6.0	3.4	250	2.6	9	0	Anemia of acute blood loss due to peptic ulcer.
18	F	49	4.18	68	6.4	4.1	255	1.3	5	0	Pericious anemia.
19	M	58	2.92	68	6.4	3.7	277	4.4	7	0	Anemia from severe epistaxis; hypertension.
20	M	58	4.80	70	5.9	3.9	287	3.0	4	0	Pericious anemia.
21	F	30	3.18	70	5.8	3.3	245	2.9	8	0	Hypochromic anemia due to bleeding hemorrhoids and malnutrition.
22	F	71	3.18	71	6.7	3.7	262	2.1	3	0	Pericious anemia.
23	M	53	4.60	73	6.5	4.0	292	2.8	7	0	Pericious anemia.
24	F	64	3.70	73	6.2	3.8	275	1.4	4	+	Anemia of acute blood loss due to peptic ulcer; hypertension.
25	M	41	3.96	76	6.3	4.3	295	1.6	4	0	Pericious anemia.
26	M	60	4.02	78	6.0	3.5	235	1.3	4	+	Convalescent pneumonia.
27	M	58	5.31	80	6.2	3.5	260	1.2	4	0	Hypochromic anemia due to bleeding hemorrhoids and malnutrition.
28	F	57	2.99	80	6.0	4.2	280	1.3	7	0	Pericious anemia.
29	F	53	5.27	88	5.7	3.2	230	0.8	4	0	Convalescent respiratory infection.
30	M	54	5.32	94	5.7	3.4	240	2.2	6	0	Peptic ulcer without blood loss.

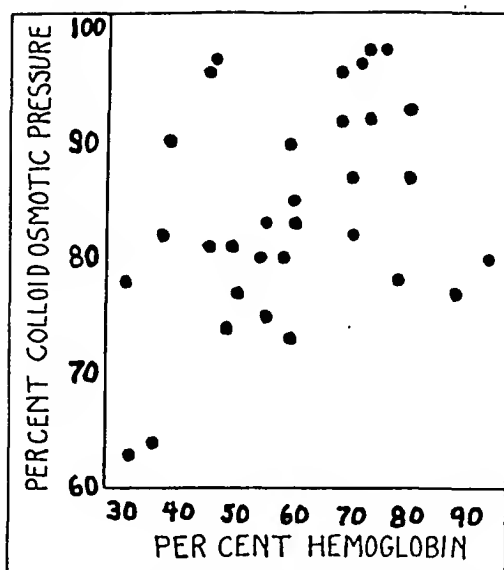


CHART 1.—The relationship of colloid osmotic pressure of the plasma proteins to the hemoglobin level. (In this and subsequent charts the hemoglobin is expressed in per cent of 15.6 gm. per 100 cc., and the colloid osmotic pressure in per cent of 300 mm.  $H_2O$ .) Correlation coefficient 0.3786.  $P = 0.05$ .

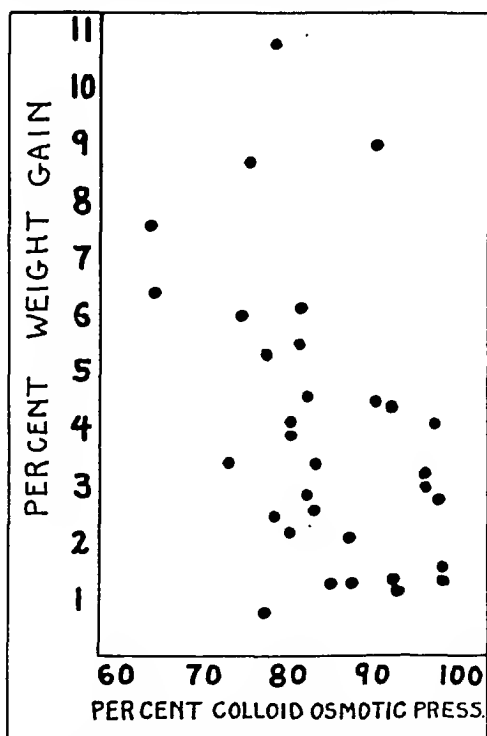


CHART 2.—The relationship of body weight gain resulting from sodium administration and the colloid osmotic pressure of the plasma proteins. Correlation coefficient 0.4990.  $P = 0.01$ .

Various formulæ were tried. One of these is shown in Chart 4, where weight gain is plotted against the product of osmotic pressure and hemoglobin. The coefficient of correlation is 0.7863 with  $P = 0.01$ , a value not significantly different from that obtained with hemoglobin alone, the probable error of the difference between these two correlation coefficients, being greater than their difference.

In addition to the above studies observations have been made on 7 additional patients. Three of these, with untreated pernicious anemia in severe relapse, received sodium bicarbonate in the same fashion as noted above. Two showed an actual loss of weight during

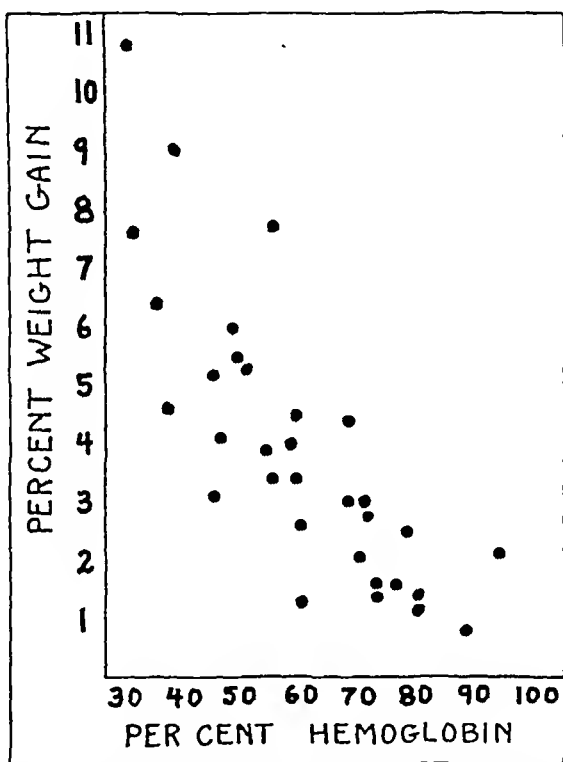


CHART 3.—The relationship of body weight gain resulting from sodium administration and the hemoglobin level. Correlation coefficient 0.7780.  $P = 0.01$ .

the administration of sodium, and the third failed to show any significant gain. All 3, however, showed significant water retention following the institution of liver therapy.

One patient with severe hypochromic anemia failed to show any weight gain while sodium was being administered but promptly lost 2% of her original weight when sodium was omitted.

Two patients with hypochromic anemia received 40 gm. of sodium bicarbonate daily. Each retained much more water than patients with similar blood levels receiving 23 gm. of sodium bicarbonate.

A patient who had gained 2% of weight while taking soda lost



this amount of weight during a period of 24 hours when he was kept flat in bed, regaining it upon again becoming ambulatory. This observation was repeated on the same patient with identical results.

One of the 26 patients reported who had hypochromic anemia associated with nutritional deficiency received 50 mg. of thiamin chloride daily by intravenous injection at the time that her water retention from sodium was most marked. The thiamin was without effect upon her weight or edema.

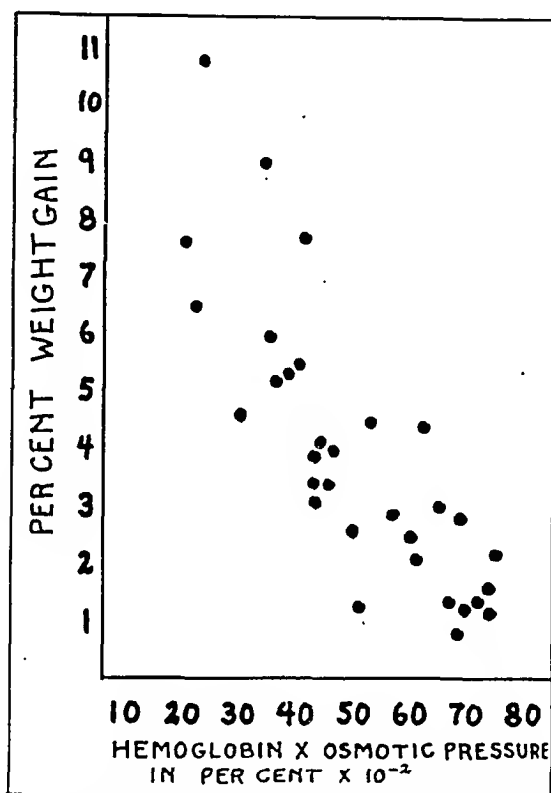


CHART 4.—The relationship of body weight gain resulting from sodium administration and the product of colloid osmotic pressure  $\times$  hemoglobin  $\times 10^{-2}$ . Correlation coefficient 0.7863.  $P = 0.01$ .

**Discussion.** Are the weight changes occurring within brief periods of time in the patients described above due to changes in water balance? Hastings, Liu, and Dieuaide<sup>4</sup> have shown that the difference between the total fluid intake (water + water in food + water of combustion of food) and the total fluid loss (urine + water of feces + water lost through lungs + insensible perspiration) closely parallels the difference in day to day weights of animals carefully studied. Gamble<sup>3</sup> has considered weight changes over short periods of time as largely due to changes in water balance, and since it is chiefly the extra-cellular water which is involved, considers that for

each kilogram of body weight gained there is retention of 147 m-eq. of sodium (approximately 4.0 gm. of NaCl per lb. of weight). The improbability of loss or deposition of any quantity of body tissue in these brief periods is a further argument for considering that the weight changes observed are largely due to water and sodium retention.

It is apparent that anemia in these cases did not lead to an elevation of venous pressure. Therefore an increased intracapillary pressure from an increased venous pressure ("cardiac weakness") cannot be responsible for the water retention observed.

There can be no question but that the plasma protein osmotic pressure plays an important rôle in water balance. However, since there was no significant correlation between the plasma protein osmotic pressure and the weight changes in these patients, it appears that lowering of the plasma proteins was not a significant factor. It should be pointed out, however, that none of the patients in this series had extremely low plasma protein values. Only 2 were below 73% of normal, these being 63 and 64% respectively. Had patients been available with very low plasma proteins, there is little doubt but that the influence of these levels would have been apparent.

The velocity of blood flow in anemia has been shown to increase proportionately to the severity of the anemia.<sup>2</sup> In Schade, Claussen and Birner's experiments it was observed that the flow of cell-free serum was two and a half times that of whole blood *when the pressure gradients were equal*. However, in patients with anemia it is conceivable that arteriolar dilatation may occur resulting in higher filtration pressures within the capillaries. No proof of this is available, nor is there any evidence that anemia leads to altered capillary permeability.

It therefore appears that anemia *per se*, through a mechanism which cannot as yet be defined, leads to a tendency to water retention. This tendency is not due to diminished plasma proteins or increased venous pressure.

In addition to the above, the failure of 3 patients with untreated pernicious anemia in severe relapse to exhibit this water retention until after specific therapy for their anemia, must be noted. This is comparable to Vaughan's observation<sup>12</sup> that in 11 of 12 patients with pernicious anemia water retention occurred spontaneously during the period between the institution of treatment and the height of the reticulocyte rise. No explanation is at hand, but it is of interest that this behavior with regard to water and sodium exhibited by patients with Addisonian pernicious anemia is not unlike that shown by patients with Addison's disease of the supra-renal capsules. The commonly observed edema of the early phase of remission in pernicious anemia as well as Vaughan's observations may possibly be ascribed to the specific effect of therapy in restoring normal salt

and water balance as well as to the common increase in salt ingestion consequent on the improved appetite of remission.

**Summary and Conclusions.** 1. Thirty-two observations have been made on 26 patients whose hemoglobin values varied from 30 to 94%. Water retention was induced in each patient by the administration of sodium salts. The magnitude of this water retention varied inversely with the hemoglobin level, the more anemic subjects showing the greatest retention. This phenomenon was not due to a concomitant lowering of the plasma protein level or to an increase in the venous pressure.

2. An exception to the above was noted in the fact that 3 patients with Addisonian pernicious anemia in severe relapse did not exhibit significant water retention during sodium administration until after the institution of liver therapy.

3. Anemia *per se* appears to be a factor conducive to water retention.

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### FAILURE TO CONTROL POLYCYTHEMIA RUBRA VERA WITH LIPOCAIC AND CHOLINE.

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PERSISTENT increase in the number of circulating erythrocytes is claimed to have been produced in animals (so-called "experimental polycythemia") by a number of methods. These have included cobalt administration, exposure to reduced oxygen tensions, and exercise. Marshall<sup>4</sup> claimed that injection of certain liver extracts would cause a temporary fall in the erythrocyte level of rats rendered polycythemic by cobalt (but that whole liver feeding exalted the polycythemia). It is maintained by Davis<sup>2a,b,c</sup> that "polycythemias" produced in dogs by the above-mentioned methods can be controlled or prevented by feeding raw liver, by the adminis-

tration of certain liver extracts by mouth and by injection, and also by feeding choline hydrochloride. The "polycythemia" produced by Davis in dogs with cobaltous chloride has been criticized by Brewer<sup>1</sup> as statistically non-significant. Major<sup>3</sup> treated 3 cases of polycythemia rubra vera with highly refined liver extracts over many months and could not demonstrate any effect. Davis suggested that the refined liver extracts employed by Major might not contain the active principle involved in reduction of the erythrocyte count. Experiences in the University of Chicago clinics have not demonstrated the usefulness of certain liver extracts in this disease. However, it has been noted on several occasions that the inception of vigorous liver therapy in cases of subacute combined degeneration of the cord with little or no anemia has been followed by a temporary but significant reduction of the red blood count.

On the basis of Davis' experimental results it was thought worth while to test, in accepted cases of polycythemia rubra vera, the effects of choline hydrochloride, and also of "lipocaiac," the pancreatic hormone shown by Dragstedt and his associates to have certain properties similar to, though far more intense than, choline in lipid metabolism.

**Methods.** The cases were selected as representing classical instances of polycythemia rubra vera. Six-tenths of a gram of choline hydrochloride daily (divided in 3 doses) was administered as representing a slightly greater dose than that used in dogs by Davis (8 mg. per kilo). This dose administered over approximately 3 weeks caused no subjective symptoms. Over similar periods the dose of lipocaiac was 12 capsules a day of an extract made available for these experiments by the kindness of Dr. Lester Dragstedt. Each capsule contained approximately 10 gr. of lipocaiac, and the dose employed is known to produce a full effect on lipid metabolism. Slight diarrhea was noted, probably due to the content of inorganic sulphates in the preparation; there were no other subjective phenomena.

**Case Abstracts.** CASE 1.—(*Choline hydrochloride.*) E. H., female, aged 56, admitted to Billings Hospital in November, 1937 (Unit No. 185897), complaining of a mass in the left upper quadrant known to be present for 2 years. Examination showed marked facial rubor, moderate clubbing of the fingers, slight proptosis oculi, and marked enlargement of the spleen. Roentgen ray of the chest showed 25% cardiac enlargement.

Clinical diagnosis: Polycythemia rubra vera.

Progress: Patient has been treated constantly with acetyl phenyl hydrazine until period of experiment.

Date,	R.B.C., millions per c.mm.	Hgb., gm. per 100 cc.	Retic., %.	Cell vol.	W.B.C. in thous.	Medication.
1937						
10/19	6.130	18.7	4.5	55	19.2	Acetyl phenyl hydrazine
1939						
4/18						Discontinue acetyl phenyl hydrazine
4/27	5.730	18.0	4.3	49	23.0	Choline hydrochloride, 0.2 gm. t.i.d.
5/1	7.300	17.5	7.5	..	17.9	Choline hydrochloride, 0.2 gm. t.i.d.
5/11	6.580	17.7	6.9	..	19.5	Choline hydrochloride, 0.2 gm. t.i.d.
5/16	5.390	15.4	1.3	51	17.0	Choline hydrochloride, 0.2 gm. t.i.d.
5/25	7.370	18.7	3.7	55	20.4	Discontinue choline
6/26	6.370	18.7	2.6	50	21.0	

CASE 2.—(*Choline hydrochloride and lipocaiac.*) C. L., female, aged 38, admitted to Billings Hospital in May, 1939 (Unit No. 220362), complaining

of recurrent tingling discomfort in first the left, then the right arm and hand, which had been variously diagnosed as erythromelalgia, Raynaud's disease, and cervical neuritis. Examination showed slight subnutritional state, moderate ocular proptosis, moderate finger clubbing, spleen palpable at the costal margin, and slight enlargement of the liver. Laboratory findings included normal chest Roentgen ray, normal hepatic function tests, B.M.R. +3%, slight reduction in vital capacity.

Clinical diagnosis: Polycythemia rubra vera.

Date, 1939.	R.B.C., millions per c.mm.	Hgb., gm. per 100 cc.	Retic., %	Cell vol.	W.B.C. in thous.	Medication.
5/15 . . .	8.400	20.2	2.0	..	10.4	Nil
6/5 . . .	8.240	20.0	1.5	..	11.8	Nil
6/16 . . .	7.400	20.0	1.0	..	..	Choline HCl, 0.2 gm. t.i.d.
6/23 . . .	7.630	20.0	0.5	..	..	Choline, as above
6/30 . . .	6.860	21.0	..	..	..	Choline, as above
7/5 . . .	6.880	20.0	..	..	..	Choline, as above
7/8 . . .	..	..	..	..	..	Discontinue choline
9/14 . . .	5.140	17.5	1.0	50	9.8	Nil
10/5 . . .	5.850	17.6	0.8	..	12.2	Nil
10/19 . . .	8.140	22.2	3.0	56.5	8.0	Choline HCl, 0.2 gm. t.i.d.
10/26 . . .	7.900	21.4	..	55	..	Choline, as above
11/2 . . .	7.330	20.4	1.2	54	..	Choline, as above
11/9 . . .	6.830	19.4	0.8	54	7.6	Choline, as above
11/16 . . .	6.770	18.8	..	54	11.0	Choline, as above
11/30 . . .	7.620	21.2	1.2	53.5	14.0	Discontinue choline
12/7 . . .	7.640	20.2	1.2	55	14.8	Lipocaiac, cap. XII daily
12/14 . . .	7.850	19.8	2.4	56	12.5	Lipocaiac, as above
12/21 . . .	7.220	19.6	0.8	52	14.4	Lipocaiac, as above
1/4 . . .	8.250	21.2	..	56	14.6	Discontinue lipocaiac

CASE 3.—(*Choline hydrochloride and lipocaiac.*) H. B., male, aged 36, admitted to Billings Hospital (Unit No. 204906) in August, 1938, with gangrene of the left leg following trauma. Slight finger clubbing, rubor facies, and marked enlargement of the spleen then noted, and count found to be 6.51 millions and 21.2 gm. of hemoglobin. Laboratory examination showed normal Roentgen ray of the chest. Leg amputated and patient treated as polycythemia rubra vera with Fowler's solution.

Clinical diagnosis: Polycythemia rubra vera. Gangrene-thrombosis of left leg.

Date, 1939.	R.B.C., millions per c.mm.	Hgb., gm. per 100 cc.	Retic., %	Cell vol.	W.B.S. in thous.	Medication.
5/2 . . .	4.800	17.7	0.83	..	4.20	Discontinue Fowler's
6/13 . . .	5.160	17.7	3.2	51	4.80	Choline HCl, 0.2 gm. t.i.d.
6/20 . . .	5.000	17.5	1.8	50	..	Choline HCl, 0.2 gm. t.i.d.
6/23 . . .	5.330	18.0	..	52	..	Choline HCl, 0.2 gm. t.i.d.
6/25 . . .	..	..	..	..	..	Discontinue choline HCl
6/29 . . .	5.350	18.0	1.43	51	5.20	Nil
9/5 . . .	5.770	16.5	3.1	48	..	Nil
9/12 . . .	6.140	18.0	1.1	53	6.60	Nil
9/19 . . .	6.160	18.7	..	51	4.50	Choline HCl, 0.2 gm. t.i.d.
9/25 . . .	5.900	17.9	1.2	54	7.20	Choline HCl, 0.2 gm. t.i.d.
10/3 . . .	6.100	18.0	..	55	6.20	Choline HCl, 0.2 gm. t.i.d.
10/10 . . .	6.260	18.7	2.1	58	..	Choline HCl, 0.2 gm. t.i.d.
10/17 . . .	5.820	18.0	3.4	51	8.50	Discontinue choline
10/24 . . .	5.840	18.0	..	54	8.90	Lipocaiac, cap. XII daily
10/31 . . .	5.870	17.3	2.0	53	9.40	Lipocaiac, cap. XII daily
11/7 . . .	5.530	19.6	1.8	51.5	7.30	Lipocaiac, cap. XII daily
11/14 . . .	5.580	16.2	..	52	..	Lipocaiac, cap. XII daily
11/21 . . .	6.400	17.7	..	54	6.80	Lipocaiac, cap. XII daily
11/28 . . .	6.760	18.7	2.3	55.5	6.50	Lipocaiac, cap. XII daily
12/5 . . .	6.400	18.0	..	57	6.40	Discontinue lipocaiac

CASE 4.—(*Lipocaiac.*) P. L., female, aged 48, admitted to the Billings Hospital (Unit No. 177125) in April, 1940, complaining of weakness, tiredness, headaches, and vomiting of 2 years' duration. She had noted recently the ruddiness of her complexion. Examination showed moderate subnutrition, facial rubor, slight finger clubbing, spleen palpable at the costal margin, slight hypertension (146/110), and moderate clinical enlargement of the

heart. Laboratory examination showed faint albuminuria with moderate reduction in renal function to the Van Slyke urea clearance test, B.M.R. +25%, slight reduction in vital capacity. Roentgen ray showed moderate cardiac enlargement with clear pulmonary parenchyma. Sternal biopsy showed hyperplastic bone marrow in all elements, with prominent megakaryocytes. Hepatic functions normal to galactose tolerance test.

Clinical diagnosis: Polycythemia rubra vera: moderate hypertension with slight reduction in renal function for further evaluation. (On hospital bed rest for 7 days, blood pressure dropped to 134/88.)

Date, 1940.	R.B.C., millions per c.mm.	Hgb., gm. per 100 cc.	Retic., %.	Cell vol.	W.B.C. in thous.	Medication.
3/18 . .	7.330	21.2	0.8	68	8.00	<i>Nil</i>
3/25 . .	7.070	20.8	1.0	70	..	Lipocaiac, cap. XII daily
3/28 . .	7.420	22.8	0.2	70	..	Lipocaiac, cap. XII daily
4/ 2 . .	7.440	23.0	..	72	8.20	Lipocaiac, cap. XII daily
4/11 . .	8.200	27.0	8.0	74	8.20	Lipocaiac, cap. XII daily
4/25 . .	7.260	22.0	2.5	70	..	Lipocaiac, cap. XII daily
5/ 2 . .	7.140	23.0	1.1	70	8.80	Lipocaiac, cap. XII daily
5/ 9 . .	8.440	26.2	0.09	73	8.90	Discontinue lipocaiac

**Conclusions.** Lipocaiac and choline hydrochloride were shown to have no effect, in doses believed adequate, on the erythrocyte level in polycythemia rubra vera over periods of up to 1 month.

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### BLOOD PRESSURE DETERMINATIONS BY PATIENTS WITH ESSENTIAL HYPERTENSION.

#### I. THE DIFFERENCE BETWEEN CLINIC AND HOME READINGS BEFORE TREATMENT.\*

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THE present knowledge of essential hypertension is based on measurements of blood pressure made by physicians, largely in the clinic or office. No data are available regarding the level of blood pressure which obtains during a patient's normal daily activities. The importance of such information for a complete knowledge of the life history of hypertension is evident.

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The present study has been an attempt to compare the blood pressure readings in the office or clinic with those taken at home by the patient or some member of the patient's household. This study has permitted the correlation of the home blood pressure levels with changes in environment, symptoms, weather, season, and so on, and also with treatment. The present paper, the first of a series on these subjects, limits itself chiefly to a report of the differences themselves between the blood pressure readings taken by the physician and those taken at home by the patient or some member of the household, in patients not under treatment.

**Material.** The present report is a study by the above method of 34 patients with essential hypertension. There were 10 males and 24 females; their ages ranged from 32 to 67 years (average 43). The average known duration of their hypertension by history was 6.2 years, and by hospital records 5 years. The patients were followed by the authors for an average period of 22 months, during which period the 34 patients made an average of 21 visits each to the clinic. At each of these visits the blood pressure was recorded before and during 20-minute rest periods. In all of these patients annual 7-foot heart Roentgen rays, electrocardiograms, and studies of renal function were made. The latter included dilution-concentration tests, routine examinations of single specimens, and intravenous pyelography.

In 18 of the 34 cases, the transverse diameter of the heart by Roentgen ray was less than 52% of the total transverse diameter of the chest, *i. e.*, well within normal limits. In 3 of the remaining 16 cases, it was over 57% of the total transverse chest diameter. In 10 of the 34 cases, there were inverted coronary-type *T* waves in Lead 1, 2, or both, while in 4 more of the 34 cases there were erect but low *T* waves in Lead 1 or 2. In the remaining 20 cases, the electrocardiograms were normal except that slight left axis deviation was present in a few. In only 2 of the 34 cases, did the ocular fundi show edema of the disks, and in 2 other cases there were small fresh hemorrhages. In all of the remaining cases there were varying degrees of arteriolar narrowing and arteriovenous nicking. In every case the renal function was good. In 26 of the 34 cases, the specific gravity of the urine was 1.024 or higher by a modified Mosenthal test, while in 13 of the 34 cases it was 1.028 or more. In no case was the specific gravity below 1.020. In 6 of the 34 cases, small amounts of albumin were noted inconstantly. Only 1 of the 34 cases was free of symptoms, while all of the others had headaches, dizziness, and other non-specific complaints.

In 16 of the 34 patients, blood pressure readings over 240 mm. systolic were occasionally found; in 13 of the 34 patients, readings over 250 mm. were occasionally noted. In 23 of the 34 patients, occasional diastolic readings in the clinic of over 130 mm. were found, and in 15 of the 34 patients, occasional diastolic readings of over 140 mm.

**Methods.** Each patient was given a mercury blood pressure manometer and a stethoscope. Either the patient or some member of the household was taught how to measure the blood pressure; those patients who determined their own blood pressure were given a special zipper cuff instead of the ordinary wrap-around cuff. The zipper cuff could be put on easily by the patient himself, thus dispensing with the need of another person for putting on the ordinary cuff. Patients were taught to regard as the systolic blood pressure the level at which the first appearance of a clear sound was noted. In the case of the diastolic reading patients were instructed to take the level of the complete disappearance of all sound as the diastolic blood pressure; this is sufficiently accurate for the purposes of this study and is easier to recognize than the more correct fourth phase. The patients were taught that the arm and blood pressure machine were to be kept on the horizontal level, the readings were to be taken in a quiet room without audience, the mercury was to be allowed to drop very slowly, and so on.<sup>1</sup> During the period of teaching, the determination of blood pressure was effected by means of a double stethoscope, so that at all times the authors heard exactly the same sounds as the patient or member of the household. All patients learned the procedure easily and thoroughly. In 13 of the 34 cases, the patients took their own readings, while in the remaining 21, some member of the household was taught to take them. The patient was instructed to make the readings twice daily; in the morning and in the evening. At each session, 4 readings were taken with intervals of at least 1 minute between readings. The average duration of each session for all patients was 12 minutes. Each patient was given special sheets of paper on which to record the readings, and was instructed also to record at each session any special symptoms or events. The patients were seen in the clinic or office at an average of once in 2 weeks. At such visits to the clinic, the patient was seated in a quiet room and the blood pressures were taken by the doctor during a 20-minute rest period, as described in previous studies.<sup>2a</sup> After this 20-minute rest period in the clinic the patient's ability to determine his blood pressure was frequently checked with the double stethoscope. This study differs therefore from that reported by Brown,<sup>3</sup> in 1930, of a patient with essential hypertension who took his own systolic blood pressure for 3 years. No correlation was made between clinic and home readings.

**Results.** More than 2800 clinic readings and 40,000 home readings were made in this study. The results will not be analyzed statistically; only obvious trends will be noted.

The average high readings (Column A, Tables 1 and 2) were usually the initial ones taken both at home and in the clinic. In 4 of the 34 cases, these average highest systolic readings were 50 mm. or more lower in the home than in the clinic; in 10 of the 34 cases, they were 40 mm. or more lower in the home, and in 15 of the 34 cases, they were 25 mm. or more lower in the home. In 8 of the 34 cases, the average highest diastolic levels in the home were 20 mm. or more lower than in the clinic, and in 12 of the 34 cases, were 15 mm. or more lower.

As a rule, the average lowest readings found (Column B, Tables 1 and 2) were those taken at the end of a 20-minute rest period in the clinic or taken last at each home session. In 4 of the 34 cases, the average lowest systolic readings were 30 mm. or more lower in the home than in the clinic; in 12 of the 34 cases, they were 20 mm. or



more lower in the home than in the clinic. These average maximal or minimal levels are not the occasional very high or low readings, but are actual average figures.

TABLE 1.—DIFFERENCES BETWEEN HOME AND CLINIC LEVELS OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN 34 CASES OF ESSENTIAL HYPERTENSION.

	A. Average highest clinic levels minus average highest home levels.	B. Average lowest clinic levels minus average lowest home levels.	C. Average clinic levels minus average home levels.	D. Average clinic levels during home study minus average home levels.	E. No. of weeks of home readings.
1	70/36†	30/14	50/25	40/16	H 13*
3	50/30	24/46	37/38	37/30	H 27
28	78/18	78/20	78/19	78/16	H 13
9	44/24	26/26	35/25	30/20	H 78
27	48/20	20/20	34/20	30/19	H 4
11P	50/20	18/20	34/20	30/18	P 30*
11H	30/0	8/6	19/3	7/-5‡	H 30
23	40/12	24/4	32/8	36/19	P 13
7	40/24	20/20	30/22	47/30	P 13
5	40/-4	16/26	28/11	35/13	H 10
21	40/8	32/10	31/9	20/7	H 17
4	36/10	-2/14	17/12	20/17	P 11
16	32/24	50/22	41/23	24/21	P 13
20	30/16	24/20	27/18	32/14	H 6
6	30/22	20/22	25/22	20/15	H 20
18	24/16	18/12	21/14	31/10	H 21
30	26/0	4/4	15/2	7/6	P 6
17	22/2	26/8	24/5	13/3	P 21
24	20/12	16/8	18/10	18/10	H 13
26	20/6	10/12	15/9	21/10	H 17
2	...§	...	...	22/15	P 4
13	...	...	...	25/12 = 1938 4/5 = 1939	H 94
34	24/14	12/10	18/12	-4/0	H 8
32	6/6	18/16	12/8	28/20	H 14
12H	14/10	0/10	7/10	12/15	H 94
12P	-20/46	-20/-4	-20/-10	5/5	P 94
14	12/16	2/6	5/11	3/3	H 4
19	10/10	0/10	5/10	4/5	P 9
8	10/2	10/4	10/3	7/-3	H 20
10	0/-24	16/4	8/-10	-1/8	H 7
22	...	...	...	5/6	P 12
15	...	...	...	7/2	P 52
29	0/-4	6/0	-3/-2	11/8	H 26
31	10/0	-10/0	0/0	-2/6	P 14
33	2/-4	4/4	3/0	0/5	H 10
25	10/2	12/8	11/5	10/5	H 15

\* H = Blood pressure determination by member of household; P = when taken by patient.

† = 70 systolic/36 diastolic.

‡ "-" Indicates clinic reading lower than home reading.

§ Indicates no clinic readings before home study.

The chart of a patient with all her clinic and home readings accurately plotted is presented in Figure 1. The data in all cases were plotted in this manner. Figure 1 (Case 1) presents the blood

pressure readings of a female, age 47, with essential hypertension of 8 years' duration. Her 7-foot heart plate, electrocardiogram, and renal function were normal. Her ocular fundi showed moderate

TABLE 2.—SUMMARY OF TABLE 1.

(Number of mm. of Hg by which clinic readings excelled home readings in 34 cases of essential hypertension.)

		Systolic, mm. Hg.								Diastolic, mm. Hg.			
		50+.	40+.	35+.	30+.	25+.	20+.	15+.	10+.	30+.	20+.	15+.	10+.
No. of cases in each column of Table 1.	A	4	10	11	15	16	21	21	26	2	8	12	18
	B	2	2	2	4	6	12	18	21	1	10	11	19
	C	2	3	5	10	13	15	21	23	1	8	10	18
	D	1	3	6	11	13	19	20	23	2	5	14	20

narrowing of arterioles and moderate arteriovenous nicking. Figure 1 is divided into 3 parts: Part 1 presents clinic readings before the start of the home study; Part 2 the home readings together with the clinic readings during this period; and Part 3 the clinic readings during the 2 years following the cessation of home study. That portion of the chart above the 130 mm. level presents the systolic variations. The systolic blood pressure in the clinic during the years 1936 to 1938 varied from 164 to 240 mm. and this range is shown between the heavy horizontal black bands. However, in Part 2, the home readings, the home systolic range was 134 to 170 mm. In Part 3, the clinic readings from 1938 through 1940, the systolic variations are between 168 and 240 mm. The maximal levels of systolic blood pressure at home were 70 mm. of mercury less than in the clinic, while the lowest resting levels of systolic blood pressure at home were 30 mm. less than the lowest levels of the clinic readings both before and after the home studies. Similar, though less marked variations occurred in the level of diastolic blood pressure. The average home readings were roughly 50 mm. systolic and 25 mm. diastolic less than the average clinic readings before or after the home study. The clinic readings during the home study were somewhat less than the clinic readings before or after the home study, but still were much higher than the home readings. During the first 2½ weeks of the home study, the home readings were higher than subsequently. In the upper part of Figure 1, Part 2, are noted the times of the catamenia and the occurrences of headaches. On 3 of the 4 occasions when headaches were present there was an associated rise in the systolic blood pressure. These occurred when the patient was having her catamenia. The highest evening home

readings in Figure 1, Part 2, are shown by the round black dots and are almost invariably the peak readings of each day.

**Discussion.** In every one of the 34 cases of essential hypertension, the blood pressure readings taken at home by the patient or some member of the household were lower than those taken in the clinic by the doctor. These differences between home and clinic readings varied markedly in each case, depending on whether the readings were made before, during, or after resting. The maximum differences between home and clinic are found when the readings are made before resting. Since the common method of taking blood pressure

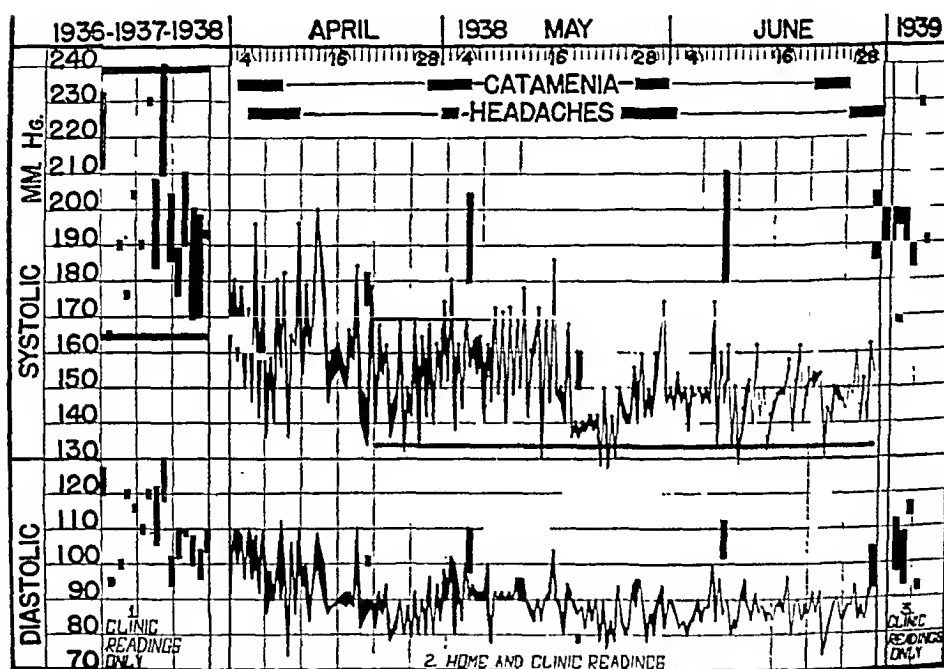


FIG. 1.—Comparison of clinic and home blood pressure readings in a patient with essential hypertension. Vertical broad black columns are clinic readings during a 20-minute rest period. Wavy lines in Part 2 are the home blood pressure readings taken by patient's daughter.

readings is to record the initial reading without rest, figures of differences between initial clinic and initial home readings here presented (Tables 1 and 2, Column A) may be applied to the experience of the general practitioner. Under such conditions, the home blood pressure level may be as much as 70 mm. of mercury systolic and 36 mm. of mercury diastolic lower than the clinic or office level (Case 1). Such great differences, as is true of all the figures in Tables 1 and 2, do not indicate occasional differences, but general ranges of blood pressure over an average period per patient of 104 weeks of special clinic study, and 23 weeks of subsequent home blood pressure study. Although the diastolic blood pressure did not vary as much as the

systolic, in 23% of the cases there was 20 mm. or more difference between the home and clinic diastolic readings. The great difference between the initial readings at home and in the clinic appears to be due to the excitement and tension associated with the visit to the clinic or doctor's office. This tension is present especially in hypertensive patients who possess a tense psychomotor makeup.<sup>2d</sup> In his home the hypertensive patient is presumably more relaxed and, therefore, his initial blood pressure reading under such circumstances is lower.

It appears reasonable that since excitement is more intense in the clinic than in the home, the clinic readings should drop the most on rest and approach closer to the home readings. The latter being taken with the patient already relaxed cannot drop very much further on rest and, therefore, home and clinic readings in this group are closer. On comparing the home reading after the patient had rested in a chair for 10 minutes or so, with the clinic reading after the patient had rested in the clinic for 20 minutes (Tables 1 and 2, Column B), the differences were, therefore, not as great as the differences between the initial readings.

In order to evaluate the possibility that during the period that the patient is taking his own blood pressure he may become calmer in the clinic in the presence of the blood pressure machine and doctor, an analysis was made of clinic readings during the period of home study. Column D, when compared with Column C shows that the average level of these readings in the clinic during home study are close to the average levels in the clinic before the home study.

It was found that the difference between home and clinic readings was in general the same in those patients who took their own readings and those who had some member of the household take the blood pressure. However, in 2 individual instances, a change from having a member of the household take it to having the patient himself take it, resulted in somewhat different levels of blood pressure being found. In 1 (Case 11) the levels became lower when the patient took his own blood pressure and in the second (Case 12) higher. The effect of different individuals on 1 patient was well illustrated in Case 25 where first one daughter, a high-strung, talkative individual, took the blood pressure. When a calmer more relaxed daughter later took over the duties of making the readings, the readings were lower. This effect of the doctor or nurse on the patient is often seen in practice where an excitable brusque doctor will cause much higher readings than a calm physician.

In the one case when a patient took his own readings and obtained higher readings than when a member of the household took them, this was due probably to the failure to relax properly. This does not indicate that he had developed a neurosis and was thereby being harmed. Indeed in no case has a neurosis developed as a result

of this study. In 1 case, however, the patient became upset when she found that her blood pressure at home was normal in the morning and high in the evening, and that she could not cause the evening readings to remain normal; in this case it was decided to stop her home study.

There were 11 cases that even in their initial systolic readings had only slight differences between home and clinic—less than 20 mm. systolic difference. These cases are the 11 cases at the bottom of Table 1. In most of these cases, the fluctuations of blood pressure during the rest period or from day to day were comparatively small. In this group of 11 cases, 2 (Cases 14 and 8) have already died of cerebral hemorrhage, while there have been no deaths in the remaining 23 patients during the  $1\frac{1}{2}$  years that have elapsed since these deaths. The 2 former patients had choked disks. One severe case (Case 10) has been helped by at least a temporarily successful sympathetic nerve resection operation. The reason for so little fluctuation in these cases is hard to understand. Four of these cases were males, while only 5 of the remaining 23 cases were males; the significance of this finding is not clear. It is to be noted, however, that in general essential hypertension seems to be more severe in the male.

VALUE OF METHOD. 1. *Teaching the Patient Knowledge of His Chronic Disease.* After weeks or months of taking their own blood pressure twice a day patients begin to understand fully some of the characteristics of their disease. They become aware that their blood pressure rises when they are under strain, worry, hard work, or hard play. One patient noted regularly that when he played cards in the evening his blood pressure was high when he arrived home despite the fact that he had not noticed himself excited during the game. Others noted the relationship of a cold house to high readings. It also has taught them how quickly high readings will drop on relaxation in a chair. They have noted the relationship of headaches and other symptoms to their blood pressure level. In general, it has seemed to make them less fearful of the disease and more prudent in their activities.

2. *Teaching the Physician.* The method also instructs the physician concerning the above points, and also gives him the opportunity to observe the natural course of the disease. It may make easier the search for the factors that adversely affect the disease.

3. *Prognosis of the Disease.* The method may possibly help in evaluating prognosis. For example, Cases 14 and 8 both had choked disks as evidence of severe disease, and both also had only slight variation between home and clinic; death occurred early in these patients. On the other hand, we feel that this method may have value in deciding the prognosis to be much better in those who have definitely lower readings at home than in the office or clinic. These much lower readings at home which we have presented in Figure 1

and Table 1 must help many physicians understand why some of their supposedly severe hypertensive patients have lived many years. The common statement that a given patient has lived 20 years with a blood pressure of 250 mm. may mean that the patient has spent most of these 20 years with a blood pressure of perhaps 170 or 180 mm., except when she sees her physician or has a momentary period of other excitement. Further data on prognosis are now being gathered.

4. *Evaluation of Therapy.* Probably the greatest value of the home blood pressure method is the evaluation of treatment. In our own attempts to evaluate treatment we have in the past<sup>2b</sup> advocated a rather elaborate method of control blood pressure readings. The home blood pressure method has given so much clearer, clean-cut results in determining the effects of treatment that this method should be considered for all clinical research in blood pressure. Data already obtained on the effects of various drugs in hypertension (which will be published separately) strongly suggest that all forms of therapy for hypertension should be restudied by this method.

It must be emphasized that these results are presented not for the purpose of having the 1,000,000 or more hypertensives in the United States secure blood pressure machines or of having the method adopted for general office use. The home blood pressure method should for the present be reserved for the occasional case in practice and for most instances of research in the treatment of essential hypertension.

**Summary and Conclusions.** Thirty-four patients with various degrees of essential hypertension had their blood pressure studied over a long period in the clinic and at home. The home readings have been very carefully taken twice daily for weeks or months by the patient or a member of the household. This study shows that the home systolic and diastolic blood pressure readings are lower than the clinic readings in all cases of essential hypertension. In 30% of the cases the systolic home blood pressure readings were 40 mm. or more lower than in the clinic, and in 24% the diastolic home readings were 20 mm. or more lower than the clinic readings. The method caused no neurosis or harm in any patient. Those patients with only slight difference between home and clinic readings had in general comparatively little fluctuation of blood pressure from day to day. The home blood pressure method should be of value to teach the patient the nature of his disease, to help the physician observe better the natural course of the disease, to aid in the prognosis of the individual case, and to permit the clear-cut evaluation of therapy.

We wish to thank the Baumanometer Company for the loan of mercury blood pressure machines, and G. P. Pilling & Sons for the loan of stethoscopes. Zipper cuffs are made by the Boullitte Company.

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## DELAYED ELECTROCARDIOGRAPHIC CHANGES IN CORONARY OCCLUSION.\*

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THE importance of electrocardiographic changes in coronary occlusion have been frequently stressed. Wilson<sup>3</sup> has, however, expressed a desirable caution in regard to their diagnostic value: "In coronary occlusion the electrocardiogram is often so characteristic that it is possible to make a positive diagnosis without other data. In general, however, it is most unwise to base any diagnosis which involves a commitment as to the presence of a coronary abnormality of any kind upon the electrocardiogram alone." Later he says: "The electrocardiogram is most useful when it is interpreted by the physician in charge of the patient." These facts are borne out in the present study in which 5 instances are reported wherein the absence of significant electrocardiographic changes in the early stages of coronary occlusion might easily have been misleading. Attention has been called to such situations in the past. Thus, Feil<sup>1</sup> states: "A normal record including chest leads should not rule out a developing coronary thrombosis," and Sampson and Eliaser<sup>2</sup> reported cases in which the electrocardiogram offered them no assistance in making a diagnosis of impending thrombosis.

**Case Reports.** CASE 1.—A. C. S., a male, aged 59, was first seen in my office August 19, 1929. He had had, 10 days previously, a sensation of pressure and heaviness over the sternum radiating down the left arm. At this time there were no findings other than a marked arcus senilis. An electrocardiogram was taken which appeared normal (Fig. 1A). He was confined to his rooms but not to bed. About 3 days later he complained of slight precordial pain. On this examination a pericardial rub and a systolic murmur at the tricuspid area were heard. The rub persisted until August 30. The temperature rose to 100.4° F. and was normal after August 30th. The leukocyte count on August 24 was 7200, with 79% neutrophils. The blood pressure was 126/84. The electrocardiogram taken on August 29, 1929 (Fig. 1B) showed relatively minor changes; on September 10, 1929, after the disappearance of the rub,  $T_1$  and  $T_2$  were rather sharply inverted (Fig. 1C). On January 31, 1930, the electrocardiogram had returned to normal (Fig. 1E).

\* Aided by the A. D. Nast Fund for Cardiac Research and the A. B. Kuppenheimer Fund.

Attack on  
8/9/29

I

II

III

A  
8/20/29

B  
8/29/29

C  
9/10/29

D  
9/20/29

E  
1/31/30

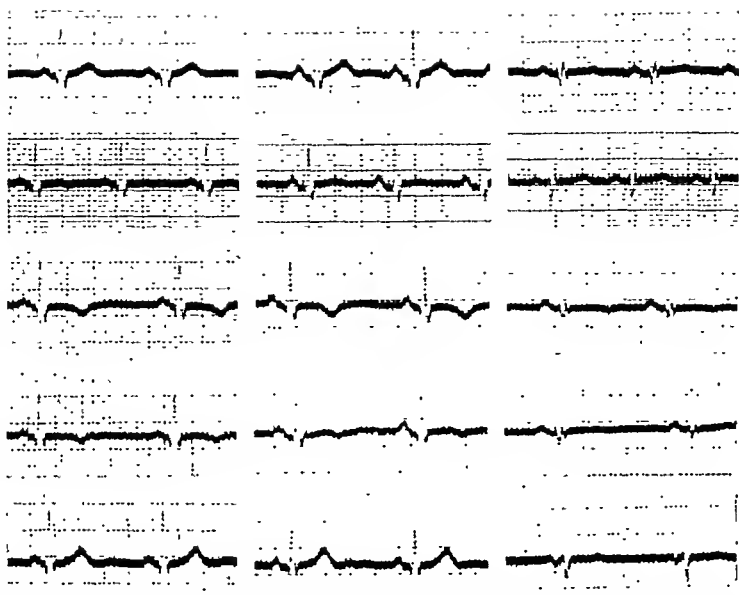


CHART 1.—Case 1. Record A was taken 11 days after the initial attack; B, 7 days after the disappearance of the rub; C, 11 days after the disappearance of the rub; D shows a slight regression and E, the return to normal.

I

II

III

CF<sub>2</sub>

A  
2/18/30

Attack on  
8/17/34

B  
8/18/34

C  
8/24/34

D  
9/7/34

E  
9/17/34

F  
9/29/34

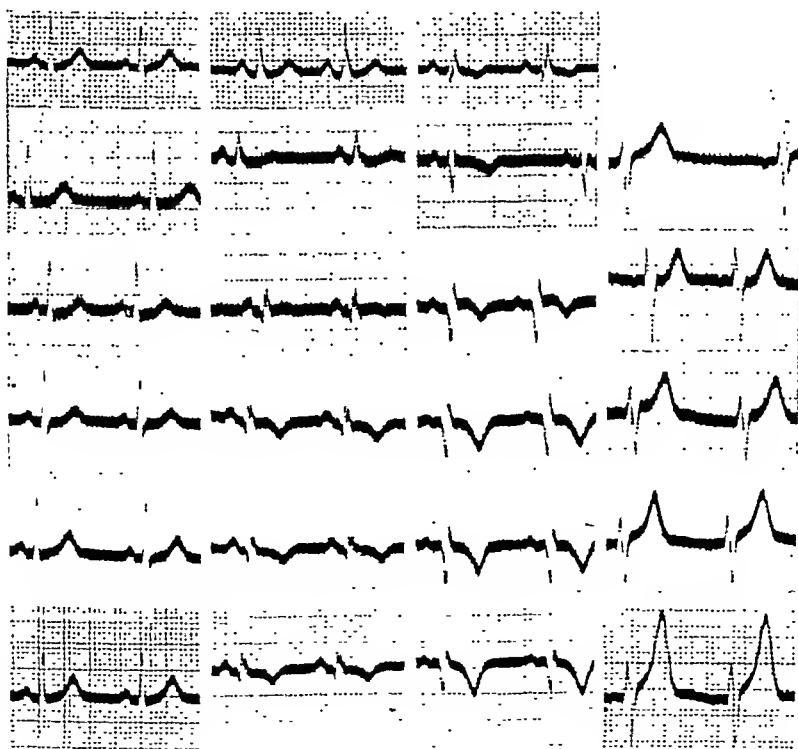


CHART 2.—Case 2. Record A was taken 4 years before the attack; B, 24 hours after the attack and C, D, E and F, respectively, 1, 3, 4, and 6 weeks after the attack.



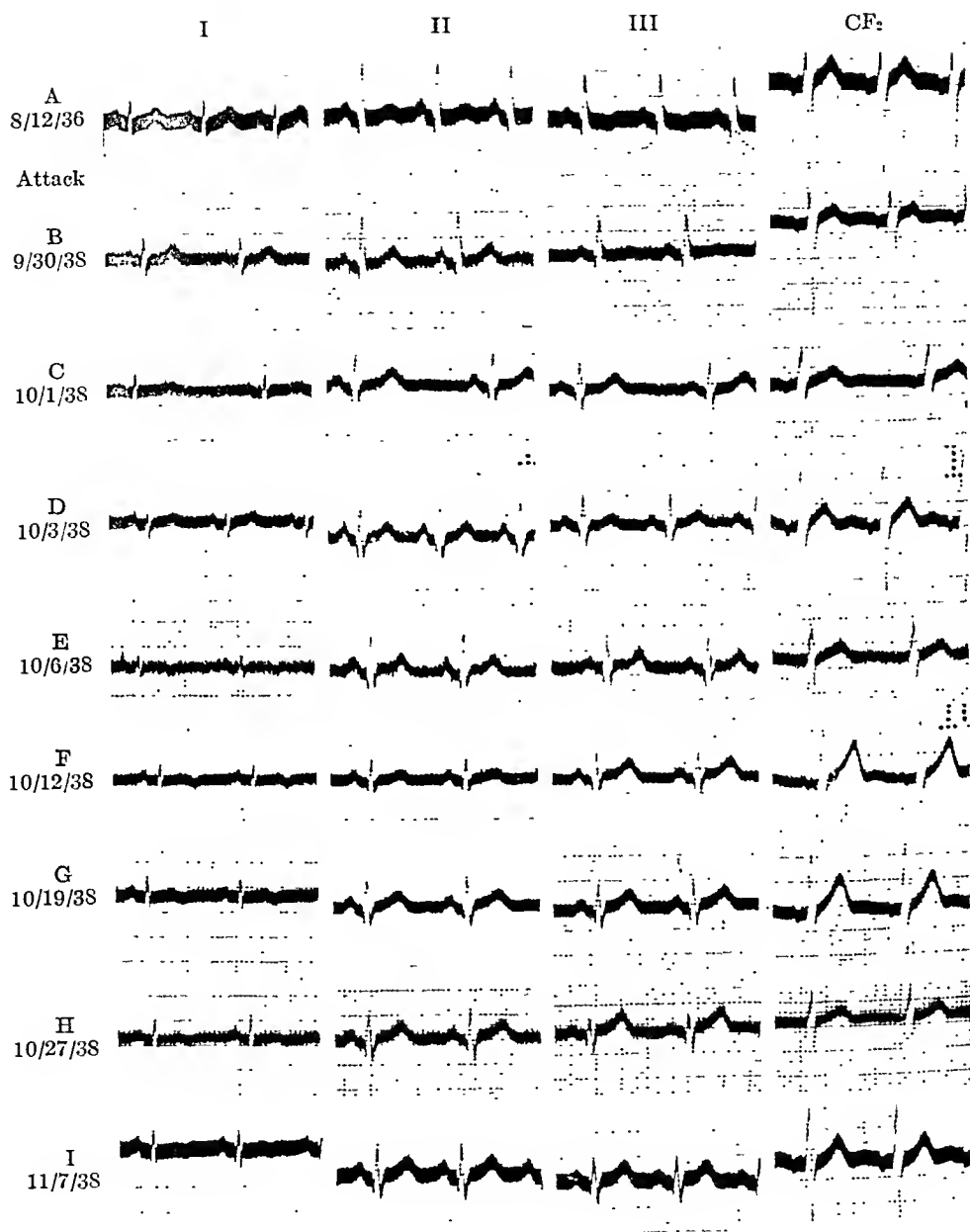


CHART 3.—Case 3. Record A was taken 2 years before the attack; B, on the day of attack and C, D, E and F, respectively, 1, 4, 7 and 13 days after the attack. G, H, I, respectively, 3, 4, and 5½ weeks after the attack.

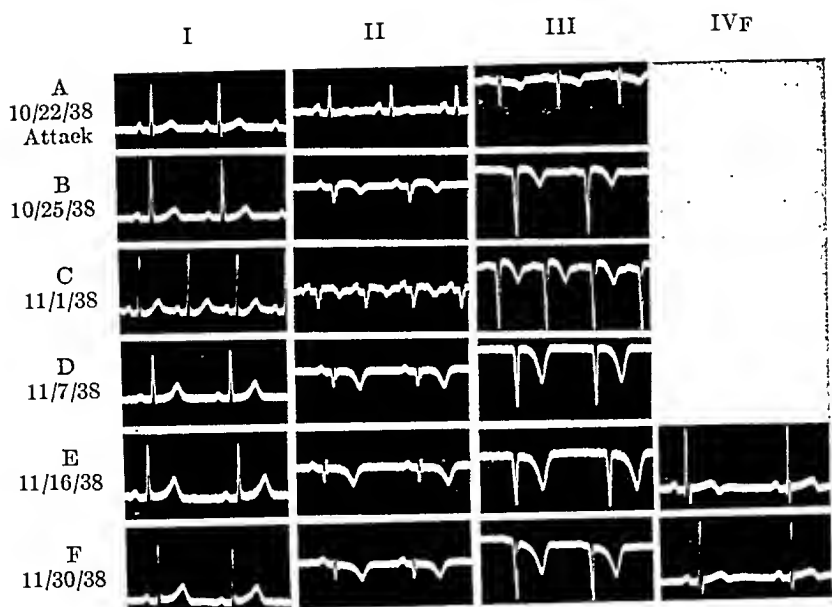


CHART 4.—Case 4. Record A was taken on the day of the onset. B shows a typical record of a posterior wall type of infarction; C, further progression; D, regression with  $S-T_2$  and  $S-T_3$  now isoelectric; E, still further regression, and F a more stabilized record.

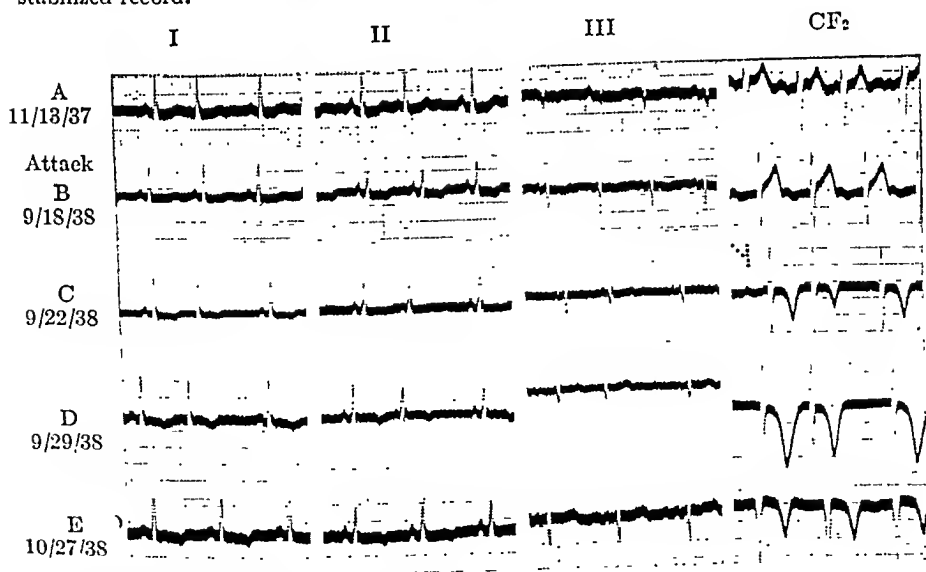


CHART 5.—Case 5. Record A was taken 10 months before the attack; B, on the day of the attack; C, 4 days after the attack and shows changes, especially in lead  $CF_2$ ; D, 11 days after the attack and shows further changes in all leads. E shows regression.



**Comment.** In this case the diagnostic electrocardiographic changes first appeared 20 days after the initial attack and 7 days after the appearance of the pericardial rub. The most marked changes occurred 19 days after the onset and 11 days after the disappearance of the rub. These electrocardiographic changes might have been due in part to pericarditis although there were never any signs of a pericardial effusion. The only reasonable cause for the pericarditis in this case was a myocardial infarct.

**CASE 2.**—S. N., a male, aged 42, when first seen at the office on February 17, 1930, complained of vise-like pain in the right chest radiating to the back. He was seen at intervals and showed no change in his condition. He was a heavy smoker and drank 3 cups of coffee a day. There was no history of alcohol. His blood pressure on these visits was approximately 135/85. At 2 p. m. on August 17, 1934 he had a moderate precordial pain radiating through to the back while walking back to his office from lunch. This gradually became worse, reaching its height at 11 p. m. At this time it was a "tight-pressing and gripping sensation over the heart." He felt weak, perspired profusely and had considerable belching. He entered the Michael Reese Hospital at 12:50 p. m. on August 18, 1934, feeling improved. At this time he stated that he had been awakened 2 months before with a sharp burning pain in the right arm radiating to the precordium and down the arm to the little finger. This was accompanied by shortness of breath. Since, then, this pain had recurred frequently during the day. It came on with exertion, lasted  $\frac{1}{2}$  hour and left a feeling of soreness.

Examination on entrance showed very few abnormalities. The apex beat was neither visible nor palpable. The heart sounds were distant and muffled. The blood pressure was 108/74; on discharge it was 112/80 and ranged from 98/68 to 118/72. On admission the patient's temperature was 98.9° F., pulse rate 64 and leukocyte count, 11,300. From August 19 to August 22 his temperature ranged from 99.6° to 102° F. and his pulse from 62 to 84. The temperature was normal on August 26 and remained so until discharge on September 29, 1934.

**Comment.** The electrocardiogram taken 24 hours after the attack showed only minor changes which could have been due to a progressive coronary sclerosis over the 4-year period which elapsed between the electrocardiograms (Fig. 2A and B). This was interpreted as such by the electrocardiographer. Later electrocardiograms (Fig. 2C, D, E and F) showed a typical posterior wall infarction of the  $Q_3T_3$  type, with healing. Symptoms and findings from the beginning were typical of a coronary occlusion.

**CASE 3.**—A. W., a male, aged 45, was first seen at the office in August, 1936, for pain in the right shoulder. His findings were negative at that time and subsequently except for a marked arcus senilis. His blood pressure ranged from 124/90 to 104/70. On September 30, 1938, he telephoned from the railroad station, saying that he had some precordial pain following exertion on the previous evening and again that morning on running for the train. These pains recurred in the office on excitement and in the hospital while taking off his shoes, being relieved each time by nitroglycerine. At 4 p. m. while in bed the pain recurred, was much more severe and lasted for over 12 hours even with morphine, and radiated to the neck and both arms. He now gave a history of having had slight precordial pain one month previously which he had ignored. With the pain at this time, there was some perspiration and pallor.

Examination showed a pulse rate of 65, no murmurs or rub and a somewhat accentuated  $A_2$ . Blood pressure at 4 P. M. was 160/110, at 9 P. M. it was 140/85. On October 1 his blood pressure was 168/108. From that time on it fell and on discharge was 110/75. The leukocyte count on October 1 was 24,000 with 74% neutrophils; on November 8 it was 11,600, with 56% neutrophils. Temperature on entrance was 99.2° F. and ranged from 98.6 to 100.8° F. up to October 6 after which it was normal. On October 3, 1938 a scratchy sound was heard during systole along the left sternal margin in the fourth and fifth interspaces. The latter can still be heard at times but is much fainter. On October 1 there was 2+ sugar in the urine; this had been absent previous to this and since that time. The blood sugar was 99. Roentgen ray showed a normal heart contour with a cardio-thoracic ratio of 12/28.3.

**Comment.** The electrocardiogram taken on the day of the attack showed practically no changes from that taken 2 years before (Fig. 3*A* and *B*). In fact, there were very few changes throughout the entire course of electrocardiographic records. The only difference of note was that  $T_1$  gradually became smaller until 2 weeks after the onset of the attack at which time it was definitely inverted (Fig. 3*F*) and this change persisted with a little waning; at the same time  $T_3$  became positive. In this instance, we have a patient with comparatively minor electrocardiographic changes, definitely out of line with the history and findings of a coronary occlusion.

**CASE 4.**—A. P., a short, obese male, aged 41, an elevator operator entered my service at the Cook County Hospital on October 22, 1938. For 2 weeks prior to entrance he had complained of fatigue and some dyspnea on exertion. On the morning of entrance while coming to work he was suddenly seized with a severe constricting substernal pain radiating to both shoulders and arms. He felt as if he would choke. He was admitted to the ward in shock, with cold, clammy skin. He was cyanotic. The pain was relieved by morphine, after several hours. Mild shock continued for several days. The findings were essentially negative. There was no fever. The blood pressure was 130/90 on entrance, 115/80 on October 24, and went as low as 90/50 on November 12. The leukocyte count was 8500 on October 23 and 15,000 on October 27.

**Comment.** The electrocardiogram taken on the day of onset of his attack (Fig. 4*A*) showed no changes other than those which could be accounted for by his stature, namely, a deeply inverted  $QRS_3$ , an inverted  $T_3$ . The diphasic  $T_2$  was unusual. Four days later, however, the changes were characteristic of a posterior wall infarction (Fig. 4*B*). Subsequent records (Fig. 4*C*, *D*, *E*, *F*) confirm this impression and show finally some regression. No chest leads were taken for the first 25 days. After this time the changes in the chest leads were insignificant as compared to the limb leads and it might be assumed perhaps without justification that this would have held true for previous electrocardiograms as well.

This is an instance in which the diagnostic changes in the electrocardiogram occurred several days after a typical onset of coronary occlusion.

**CASE 5.**—J. G., a female, aged 63 was seen by me in November, 1937. At this time she had a hemorrhage from the rectum which was and is of unknown etiology. She gave a history of having had high blood pressure

which at the time of this examination was 226/118. There were numerous extrasystoles of auricular origin giving a trigeminus.  $A_2$  and  $P_2$  were both accentuated. The heart was normal in size and shape as shown by percussion and fluoroscopy. The thoracic aorta was diffusely dilated. On September 18, 1938, she again entered the hospital. She had had an attack of epigastric pain on September 13, diagnosed as angina. This recurred on September 14, and was diagnosed as "gas" and had appeared intermittently since then, always relieved by nitroglycerine. On the morning of the 18th, these pains became severe and constant and radiated to the back and both arms and were *not* relieved by nitroglycerine but were partially relieved by morphine. She was brought to the hospital in an ambulance and upon entrance had a cold sweat, a weak pulse and nausea. These lasted for only 2 minutes when the pulse became full and bounding with a rate of 96. The heart was of the same size as on the last admission.  $A_2$  was loud and ringing. There was a systolic murmur over the pulmonic area and a fainter one over the aorta. Occasional extrasystoles were present. The next day the interne heard a friction rub. A pulsus bigeminus occurred which cleared up with atropine, gr. 1/200. This also relieved to some extent the nausea and the "indigestion" pains radiating to both arms. On November 20 she was sent home though she still had epigastric pain radiating to both arms. There was no fever at any time during the hospital stay and her blood pressure ranged from 108/70 on October 17 to 178/124 on September 21. The leukocyte count was normal. The blood pressure taken at her home on January 14, 1939, was again 230/120. She has continued to complain of epigastric pain radiating to both arms.

**Comment.** This patient at no time gave a clear clinical picture of coronary occlusion. Her symptoms and the electrocardiographic changes shown in the series of records in Figure 5 make it appear fairly certain that she had a coronary occlusion. However, the electrocardiographic changes did not appear until 4 days after the attack (Chart 5C). The changes between *A* and *B* could have been due to progressive coronary sclerosis. Furthermore, there were mild anginal attacks 4 days before the severer one without any changes in the electrocardiogram. This case is in accord with the findings of Feil<sup>1</sup> and Sampson and Eliaser.<sup>2</sup>

**Summary.** Five cases are reported in which the diagnosis of coronary occlusion was clear clinically from the start, the electrocardiograms showing changes only after a lag of several days. In 1 instance (Case 3) the changes were minimal and not definitely diagnostic without the patient's history.

**Conclusions.** 1. An adequate history is all-important in the diagnosis of coronary occlusion, as in all diseases.

2. The diagnosis cannot be left to the cardiographic laboratory alone but must be made by the clinician on the basis of all the available data.

3. Negative or inconclusive electrocardiographic findings do not exclude the presence of a coronary occlusion.

I wish to express my appreciation to Dr. L. N. Katz for his valuable suggestions in preparing this report and to Miss B. Phillips for her technical assistance.

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## CARDIAC AND RESPIRATORY FUNCTION AT REST IN PATIENTS WITH UNCOMPLICATED POLYCYTHEMIA VERA.

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POLYCYTHEMIA vera is associated with a marked increase in the volume and viscosity of the blood, changes which should influence hemodynamics to a considerable degree. All observers are in agreement that slowing of the peripheral blood flow occurs;<sup>10a,b,11,45</sup> the clinical manifestations of the disease are regarded as secondary to retardation of the rate of blood flow.<sup>21</sup> The possible effects of the hematologic changes of polycythemia vera on cardiac function have been discussed by a number of authors with divergent conclusions. Thus Goldsmith<sup>18</sup> states that the cardiac output is abnormally high, due probably to the very large blood volume, and Burton-Opitz<sup>12</sup> concludes that the cardiac work is increased as a result of increased viscosity of the blood. Other authors, however, have recorded data indicating that both are normal. It was therefore considered desirable to study the cardiovascular dynamics of polycythemia vera before and after treatment; because of the close relationship between cardiac and pulmonary function, studies of the respiration have also been made. A large number of publications bearing on this problem are available; since there is no adequate review of this literature in the English language, discussion of the cardiovascular dynamics of polycythemia vera will include reference to these reported data as well as to the findings of the present study.

**Materials and Methods.** Three patients, ranging in age from 38 to 48 years were studied; 2 were males. Only relatively young patients without hypertension were selected for study in order to isolate to as great a degree as possible the effects of the polycythemia itself. In 2 patients (Cases 2 and 3) studies were made before treatment had been instituted and again after the red blood cell count and hemoglobin had been brought to approximately normal levels by means of repeated venesection.

All measurements of cardiovascular or respiratory function were made with the patient in the post-absorptive state under basal conditions in the semi-recumbent position after a rest of from  $\frac{1}{2}$  to 1 hour. The cardiac output was measured by the ethyl iodide method of Starr and Gamble,<sup>42</sup> the pulse rate, basal metabolic rate, respiratory quotient, alveolar air carbon dioxide content and respiratory rate and minute volume being determined at the

same time. The values reported represent the average of the results of several determinations. The arteriovenous oxygen difference was calculated from the oxygen consumption and the cardiac output. Following the determination of the cardiac output the arterial blood pressure was measured. The figures in the tables represent the averages of several readings. The venous pressure was then determined by the direct method of Moritz and von Tabora.<sup>38</sup> Following this the velocity of blood flow was estimated, using as an index the "arm-to-tongue" circulation time as measured with decholin.<sup>16</sup> Finally the vital capacity was measured.

The following methods were employed in the hematologic studies: for hemoglobin, that of Haessler and Newcomer;<sup>20</sup> for blood volume, that of Keith, Rowntree and Geraghty;<sup>28</sup> for viscosity, that of Hess;<sup>23</sup> for hematocrit, that of Wintrobe.<sup>41</sup> The values reported are the averages of 2 or more measurements. Most of the hematologic studies were made on the same day as the cardiovascular and respiratory measurements; a few were made several days earlier or later.

**Observations.** All 3 patients studied before treatment showed striking increases above normal in red blood cell count, hematocrit, and blood volume and viscosity; the cardiovascular and respiratory functions measured at this time were, however, within normal limits (Table 1), with the exception of a slight elevation in basal pulse rate. No striking changes in cardiovascular and respiratory dynamics, except for some slowing of the basal pulse rate and in 1 case some acceleration of the arm-to-tongue circulation time occurred as a result of changes in the blood to or toward normal (Table 1) in the 2 patients studied after treatment.

TABLE 1.—DATA ON 3 CASES OF POLYCYTHEMIA VERA.

	Case 1.	Case 2.		Case 3.	
	Before treatment.	Before treatment.	After treatment.*	Before treatment.	After treatment.†
Sex . . . . .	F	M		M	
Age, yrs. . . . .	38	44		39	
Blood volume, cc per kg. . . . .	136	132	81	137	
Red blood cell count per c.mm. . . . .	8,370,000	9,900,000	6,900,000	7,940,000	5,810,000
Hemoglobin, gm. per 100 cc. . . . .	17.8	23.8	13.8	24.2	15.2
Hematocrit, % cells . . . . .	66	76	49	72	53
Mean cell volume, c.mm. . . . .	79	77	71	91	91
Viscosity . . . . .	10.0	15.3	6.7	10.0	6.1
Alveolar air CO <sub>2</sub> , % . . . . .	4.8	5.2	5.6	5.8	5.8
Basal metabolic rate, % . . . . .	+3	+16	+12	-15	-8
Respiratory quotient . . . . .	0.81	0.80	0.83	0.83	0.85
Respiratory rate per minute . . . . .	12	18	15	18	14
Respiratory minute volume, liters per sq. meter per minute . . . . .	3.0	4.0	3.5	3.4	3.3
Vital capacity, liters per sq. meter per minute . . . . .	1.5	2.4	1.8	1.7	2.1
Cardiac minute volume output, liters per sq. meter per minute . . . . .	2.3	2.1	2.1	2.2	2.2
Arterio-venous O <sub>2</sub> difference, vol. % . . . . .	5.61	7.41	7.36	5.16	5.60
Pulse, beats per minute . . . . .	89	78	66	79	60
Circulation time, seconds . . . . .	13	18	15	14	15
Venous pressure, cm. H <sub>2</sub> O . . . . .	3.1	9.6	6.5	9.3	9.8
Arterial pressure, mm. Hg . . . . .	120/70	135/80	135/80	120/80	110/80

\* Ten weeks later.

† 17 weeks later.

**Discussion.** 1. *Cardiac Output.* The cardiac output at rest has been reported within normal limits by a number of workers using older, inaccurate methods<sup>6,30,36,40</sup> as well as by authors using methods acceptable today;<sup>14,17,29</sup> a total of approximately a dozen patients



have been studied. Goldsmith's<sup>18</sup> findings of a markedly increased cardiac output in 2 of the 4 patients studied by her is difficult to explain, although it is to be noted that in the one patient most thoroughly studied a close correlation between cardiac output and basal metabolic rate existed, so that the increase in minute volume output of the heart must have been related to the increased metabolism. Brooks<sup>9</sup> obtained normal values for cardiac output in 1 of 2 patients studied. The other, who showed a considerable increase in cardiac output was clearly one of secondary polycythemia with marked pulmonary disease, clubbing of the fingers, incapacitating dyspnea, carbon dioxide retention and a striking decrease in arterial blood oxygen saturation; the validity of estimations of cardiac output by a foreign gas method in patients with severe pulmonary disease is questionable.

The results of the present study are in agreement with those of the majority of workers in this field: the cardiac output at rest in polycythemia vera is normal.

2. *Cardiac Work.* The work of the left ventricle is readily calculated from the formula of Evans and Matsuoka<sup>15</sup> as follows:

$$W = OP + \frac{wV^2}{2g}$$

where  $W$  = work,  $O$  = output,  $P$  = arterial resistance (mean blood pressure  $\times 13.6$ ),  $w$  = weight of the blood,  $V$  = velocity of blood in the aorta, and  $g$  is the gravitational constant. In ordinary usage the factor  $\frac{wV^2}{2g}$  is disregarded since it usually comprises no more than 1 to 3% of the total work of the left ventricle.

Since the cardiac output and the blood pressure are normal in uncomplicated polycythemia vera, it is clear that the work of the heart, at least in the resting subject, is normal.

3. *Pulmonary Circulation Time.* The pulmonary circulation time parallels the cardiac output but is also an indication of the degree of pulmonary engorgement.<sup>2,3</sup> The arm-to-tongue time may be normal<sup>17,25</sup> or slowed.<sup>4,8,25,43</sup> Tarr<sup>43</sup> *et al.* found values of 18 seconds in 2 cases and considered them prolonged; these values are probably within normal limits. Similarly the ether time may be either normal<sup>4,25</sup> or prolonged.<sup>25</sup> In the present study normal values were found in all 3 patients, although a significant acceleration occurred after treatment in 1 case.

4. *Venous Pressure.* The venous pressure was normal in all studies in the present investigation, agreeing with the findings of previous workers.<sup>17,25</sup>

5. *Lung Volume and its Subdivisions.* The respiratory rate and minute volume may be increased in patients with polycythemia vera, especially in those with elevation of the basal metabolic rate. The residual air is normal or slightly increased<sup>9,22</sup> as is the midcapacity.<sup>22</sup> Considerable difference in values for vital capacity have been recorded by various workers: Isaacs<sup>27</sup> and Brooks<sup>9</sup> found it low,

Blumgart *et al.*<sup>8</sup> found it low in 1 case with heart disease and normal in an uncomplicated case, while other authors<sup>22</sup> have reported normal values. In the present study normal values were found in 2 cases and a slight diminution in 1. No change was effected in the 2 treated cases by therapy. Brooks<sup>9</sup> reported a similar finding in a patient with diminished vital capacity. It seems unlikely, therefore, that the low vital capacity found in some patients with polycythemia vera is due directly to the increased blood volume and viscosity.

Since the vital capacity is an important part of the total lung volume, reported values for the latter can be expected to differ according to whether the former is normal or low. Thus Harrop *et al.*<sup>22</sup> reported normal values for total capacity, while Brooks<sup>9</sup> found it diminished in his 1 case of polycythemia vera.

6. *Blood Oxygen Content and Saturation.* An important indication of the functional capacity of the lungs is the oxygen saturation of the arterial blood. All authors<sup>6,9,22,24,36,40</sup> report normal values; the capacity is greatly increased but the content increases in proportion. The finding of Harrop *et al.*<sup>22</sup> that the arterial oxygen saturation decreases after exercise is difficult to explain unless exercise induces in polycythemic patients extremely rapid shallow breathing.<sup>34</sup> The venous blood oxygen saturation is within normal limits;<sup>27,32,37</sup> here again the capacity is elevated and the content is also increased. Since the arterial and venous blood oxygen contents are increased to the same degree, the arterio-venous oxygen difference must be normal.

7. *Blood Carbon Dioxide Content and Combining Power.* The carbon dioxide combining power in polycythemia vera is rather low<sup>27</sup> as is the carbon dioxide content of the venous blood.<sup>32,37</sup> This is due at least in part to the fact that the blood cells contain only about 60% as much available base as serum. Since a given unit of polycythemic blood contains as much as 70 to 80% cells, as compared to the normal value of 45%, it is clear that lowering of the whole blood carbon dioxide content and combining power must occur although there is no detectable abnormality in the electrolyte pattern of the serum.

Another factor contributing to a lowered blood carbon dioxide content may be hyperventilation due to stimulation of the respiratory center by factors other than carbon dioxide retention; this will be discussed elsewhere.

8. *Basal Metabolic Rate.* The metabolic rate may be high,<sup>1,7,9,17,18,21,26,27,31,33,35,40,41</sup> normal,<sup>5,6,7,14,18,19,21,33,40</sup> or occasionally low<sup>29</sup> in patients with the disease. In the present study the metabolism was essentially normal in all instances and was not influenced by therapy. Bliss<sup>7</sup> treated 10 patients and found no consistent change in basal metabolic rate. Goldsmith's<sup>18</sup> patient with an elevated basal metabolic rate showed some decrease after treatment while Brooks'<sup>9</sup> showed no change. The cause of the increase in metabolic rate in polycythemia vera is not definitely known but it may be the

increased respiratory activity of some patients. Resnik and Friedman<sup>39</sup> have shown that increased respiratory activity in patients with congestive failure is associated with elevation of the basal metabolic rate; a similar situation may exist in polycythemia vera.

9. *Capillary Blood Flow.* The velocity of capillary blood flow as visualized in the nail beds is greatly diminished.<sup>10a,b,11,45</sup> The capillaries are elongated, tortuous, and, especially in the venous segments, greatly distended. The small venules are also engorged. The blood cells move through the capillaries in broad columns instead of single file.

A similar phenomenon is observed in congestive failure,<sup>2</sup> but is associated with a diminished cardiac output. In polycythemia vera, however, the output of the heart is normal and the slow flow observed must therefore be due to peripheral factors. The marked vasodilation which is due to increased blood volume can account for some of the slowing. Nevertheless, a normal amount of blood enters each part of the body via the arteries and leaves via the veins, as evidenced by the normal values found for cardiac output and arteriovenous oxygen difference. An explanation for the occurrence of this phenomenon in spite of marked slowing of blood flow is the considerable increase in blood volume observed in polycythemia vera. The slowing of blood flow due simply to capillary dilation is not physiologically important in this disease since its effects are counteracted by increased blood volume. Indeed, it is possible that the vasodilation is merely secondary to the increased blood volume.

There is no mechanism completely balancing the action of increased blood viscosity in slowing the capillary blood flow. Poiseuille's law states that if the force remains the same, the velocity of a moving liquid in a capillary varies inversely as the viscosity. Other factors also influence the velocity, as can be seen from the formula.

$$v = \frac{\pi r^4 P}{8\eta l}$$

where  $v$  = velocity,  $r$  = radius of the capillary,  $l$  = length of the capillary,  $\eta$  = viscosity of the liquid and  $P$  = propelling pressure. Thus dilatation of the capillaries counteracts to some extent the effect of viscosity and lengthening the capillary exaggerates it. It is to be noted however<sup>10a,b,11,45</sup> that there is little or no dilatation of the arterial loop of the skin capillaries in polycythemia vera, so that the marked dilatation of the venous limbs of the capillaries does not serve to counteract the slowing effect of the blood viscosity as much as it might.

The applicability of Poiseuille's law, based on studies on systems of rigid tubes, to conditions within the animal body has been questioned but the experiments of du Bois-Reymond<sup>13</sup> on isolated animal organs clearly demonstrate the validity of Poiseuille's conclusions when applied to the elastic vessels of the animal body.

The only striking abnormal cardiovascular finding resulting from available studies on polycythemia vera is marked slowing of periph-

eral blood flow. The data obtained in the present study, together with the findings of other authors here reviewed, indicate that cardiac output and work are normal in patients with polycythemia vera, at least at rest. It must be concluded, therefore, that the increased volume and viscosity of the blood impose no abnormal burden on the heart. A corollary to this conclusion is that the slow peripheral blood flow of polycythemia vera is due solely to peripheral factors. Studies of the physiology of the peripheral vascular system in this disease will be the subject of another communication.

**Summary and Conclusions.** 1. Measurements of cardiac and respiratory function in patients with polycythemia vera at rest are normal.

2. The slowing of blood flow, and the symptoms associated with it, are not due to impaired cardiac function but rather to increased resistance to the flow of blood through the small capillaries. This is due largely to increased viscosity of the blood.

The patients used in this study were very kindly referred to us by Dr. William Dameshek.

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MANOMETRIC DETERMINATION OF THE EFFECTS OF  
VARIOUS SULFANILAMIDE COMPOUNDS ON  
BRUCELLA MELITENSIS.

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THE rapid development of sulfanilamide derivatives has made it desirable that accurate methods be established for the evaluation of the bacteriostatic or bacteriocidal potency of these drugs. Up to the present time the standard bacteriologic methods for culturing and counting organisms have been used. Such methods have several obvious disadvantages. Constant conditions of  $O_2$  and  $CO_2$  tension, pH and so on, cannot be maintained during the course of the experiment. Observation of growth after transfer of the drug-affected culture to fresh drug-free optimal media tells nothing about the condition of the bacteria during the period of exposure to the drug. The bacteriologic methods of culturing and counting cannot be applied without interrupting the actual experiment. Each time that data are required concerning the effects of the drug upon the bacteria, the original culture tube must be opened, or a separate control culture tube must be used, for determining each single point of the growth curve. It is true that the inaccuracy inherent in variations in the inoculum can be minimized by the use of the photronreflectometer, by which means the initial number of bacteria used for primary inoculation of the culture tubes can be accurately determined, and subsequent comparative determinations of the number of bacteria can be made. No information, however, is obtained by this method as to the state of the bacteria, for the density of cultures may be the same whether the bacteria are living or dead.

The measurement of the chemical reactions of the bacteria by the manometric technique of Warburg<sup>7</sup> is at present the most accurate and sensitive method available for measuring increases or decreases in bacterial metabolism. Such manometric determinations can be carried on for many days with the original culture in the same vessel and, since readings can easily be made every 5 or 10 minutes, the reaction of the bacteria with the drug is continuously observable and quantitative data are available for every

growth period. Constant conditions of  $O_2$  and  $CO_2$  tension, pH, and so on, are maintained throughout the experiment and there is no variation of the bacterial density in different layers of the cultures. Furthermore, the actual reactions of the bacteria are measured during the period of exposure to the drug, thus simulating conditions analogous to those existing *in vivo* during a period of drug administration.

In view of the differences in the effectiveness of the various sulfanilamide compounds with regard to different species of bacteria and different strains of the same species, it seems desirable to try to obtain exact quantitative data on as many single bacterial strains as possible. In this paper we are reporting only that part of our work which deals with the effect of various sulfanilamide compounds on a strain of *Brucella melitensis* var. *melitensis*. (For complete bibliography on the action of sulfanilamide and allied compounds on brucella, see Long and Bliss;<sup>3</sup> Mellon, Gross and Cooper;<sup>4</sup> Menefee and Poston;<sup>5</sup> Green.<sup>1</sup>)

**Technique.** The strain of *Brucella melitensis* used was obtained from Dr. I. F. Huddleson. Beef infusion—m/28 to m/40 phosphate pH 7.4—broth and human serum of normals and of patients were used as culture media. The age of the bacteria inoculated was from 10 to 120 hours. The culture density at the beginning of the experiment was varied between 100,000 to 40 million organisms per cc. The high density was chosen to shorten the duration of the experiments and to test the difference in effectiveness of the various drugs with regard to maximal infections. Two cubic centimeters of the bacteria-broth-phosphate suspension were pipetted into conical manometer vessels of about 18 cc. capacity and drug solutions (0.07 to 0.14 cc.) were added to make final concentrations of 0.5 to 10 mg. per 100 cc. The oxygen concentration was that of air. The side bulbs of the vessels contained KOH to absorb the carbon dioxide. The manometers were placed in a thermostat at 38° C. and shaken at a rate of 80 to 220 oscillations per minute. Readings were made without stopping the manometers, and the oxygen consumption was measured and calculated according to Warburg.<sup>7</sup> The density determinations were made with the photron-reflectometer (Libby<sup>2</sup>). The weight of the bacteria was determined according to Peschel.<sup>6</sup>

We found the dry weight of 100 million organisms to be about 1.6 mg., the average oxygen consumption of 1 mg. dry weight of *Brucella melitensis* in phosphate broth pH 7.4/air per hour,  $QO_2 = 168$  c.mm.; of 100 million brucella organisms per hour,

$$\frac{O_2 \text{ consumption}}{100 \text{ million organisms} \cdot \text{hour}} = 1.4 \text{ c.mm.}$$

(40 determinations).

The drugs tested were: sulfanilamide (p-aminobenzene-sulfonamide, Merck), sulfapyridine sodium (sodium 2-sulfanilyl aminopyridine monohydrate, Merck), sulfathiazol (2-sulphanilamido-thiazol, Winthrop), sodium disulon (sodium sulfanilyl sulfanilamide, Alba Pharmaceutical Co.), benamide (p-caproylaminobenzene-sulfonylhydroxamide, Sharpe & Dohme), promin (sodium salt of p,p'-diaminodiphenylsulfone-N,N'-di(dextrose sulfonate, Parke, Davis Co.), sulfamethylthiazol (2-sulphanilamidomethylthiazol, Winthrop).

**Results.** Figure 1 illustrates a typical experiment on the effect of sulfanilamide, sulfapyridine sodium, sulfathiazol and sulfamethyl-

thiazol, in concentrations of 5 mg. per 100 cc. each, on the rate of growth of a phosphate broth culture of the Huddleson strain of *Brucella melitensis*. The initial bacterial density as determined by the photoreflexometer was 30 million organisms per cc., so that each of the 5 test vessels contained 60 million organisms (2 cc. suspension).

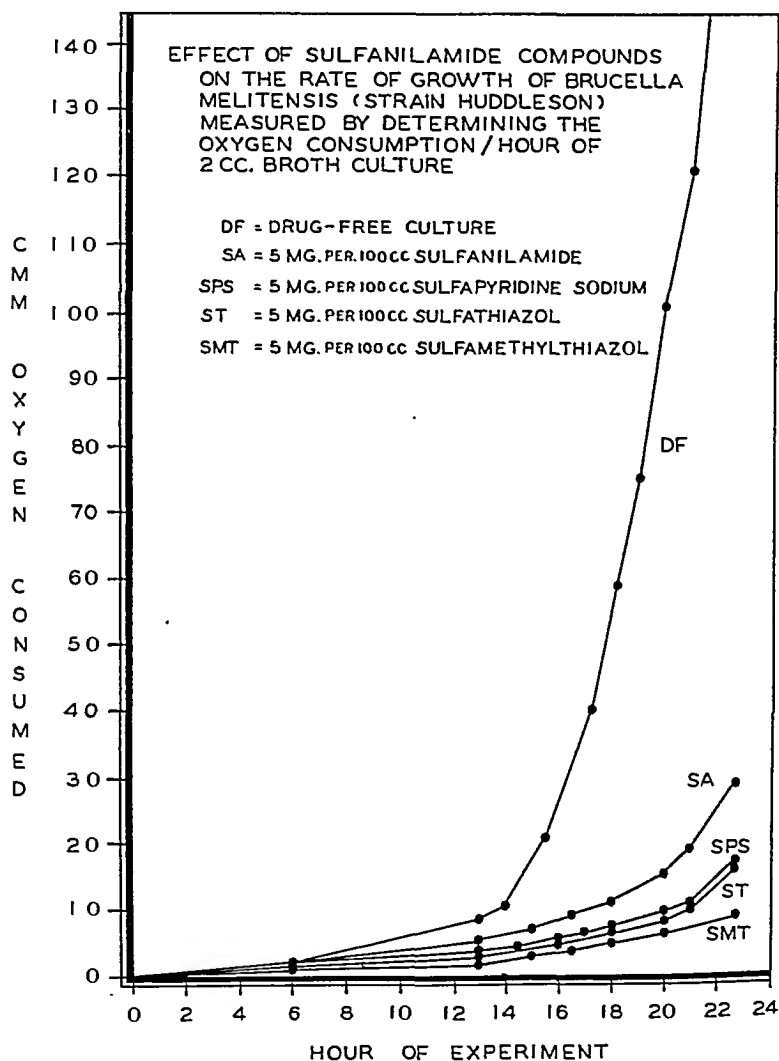


FIG. 1.

According to the average metabolism figures of 1.4 c.m.m.  $O_2$  per hour for 100 million brucella organisms, as given above, the culture in each vessel should have shown an oxygen consumption per hour of

$$1.4 \cdot 2 \cdot \frac{30}{100} = 0.84 \text{ c.m.m. } O_2,$$

provided no growth took place. During the first 12-hour period of the experiment the average oxygen consumption per hour was as follows:

Drug-free culture . . . . .	1.77 c.mm. O <sub>2</sub>
Sulfanilamide culture . . . . .	1.72 c.mm. O <sub>2</sub>
Sulfapyridine sodium culture . . . . .	1.77 c.mm. O <sub>2</sub>
Sulfathiazol culture . . . . .	1.64 c.mm. O <sub>2</sub>
Sulfamethylthiazol culture . . . . .	0.94 c.mm. O <sub>2</sub>

It is, then, evident that some growth did occur in each of the cultures as early as within the first 12 hours. The rate of growth was the same in the sulfanilamide, sulfapyridine sodium, and sulfathiazol cultures as in the drug-free control; whereas in the sulfamethylthiazol culture, even at this early stage, growth was definitely inhibited. Compared to the oxygen consumption of the initial 60 million organisms, the oxygen consumption in sulfamethylthiazol was only increased by 12%, in the 4 other cultures by 95 to 111%.

Eighteen hours after the beginning of the experiment, the differences between the drug-free and the drug-containing cultures appeared more clearly. The oxygen consumption per hour was:

Drug-free culture . . . . .	59.00 c.mm. O <sub>2</sub>
Sulfanilamide culture . . . . .	10.80 c.mm. O <sub>2</sub>
Sulfapyridine sodium culture . . . . .	7.85 c.mm. O <sub>2</sub>
Sulfathiazol culture . . . . .	6.80 c.mm. O <sub>2</sub>
Sulfamethylthiazol culture . . . . .	4.97 c.mm. O <sub>2</sub>

*i. e.*, in the drug-free control it was 70 times as high as at the beginning of the experiment—59 against 0.84 c.mm. O<sub>2</sub> per hour—in sulfanilamide 12.9 times, in sulfapyridine sodium 9.35 times, in sulfathiazol 8.1 times, in sulfamethylthiazol 5.9 times as high. That means that after an observation period of 18 hours, the inhibition of the brucella growth rate was: by sulfanilamide of 81.7%, by sulfapyridine sodium of 86.7%, by sulfathiazol of 88.5%, by sulfamethylthiazol of 91.6%.

In the 23d hour the absolute figures of oxygen consumption per hour were:

Drug-free culture . . . . .	210.0 c.mm. O <sub>2</sub>
Sulfanilamide culture . . . . .	28.8 c.mm. O <sub>2</sub>
Sulfapyridine sodium culture . . . . .	17.2 c.mm. O <sub>2</sub>
Sulfathiazol culture . . . . .	16.0 c.mm. O <sub>2</sub>
Sulfamethylthiazol culture . . . . .	8.5 c.mm. O <sub>2</sub>

*i. e.*, the oxygen consumption per hour in the drug-free control was 250 times higher than at the beginning of the experiment, in sulfanilamide 34.3 times, in sulfapyridine sodium 20.5 times, in sulfathiazol 19.1 times, in sulfamethylthiazol only 10.1 times higher. Using an identical concentration of 5 mg. per 100 cc. for the four drugs, the inhibiting effect of sulfapyridine sodium was 67% greater than that of sulfanilamide, the effect of sulfathiazol 7% greater than that of sulfapyridine sodium, the effect of sulfamethylthiazol



88% greater than that of sulfathiazol, 102% greater than that of sulfapyridine sodium, and 240% greater than that of sulfanilamide.

The cell counts measured with the photonreflectometer at the end of the experimental period of 23 hours, were as follows:

Drug-free culture . . . . .	12,960 million organisms
Sulfanilamide culture . . . . .	1,990 million organisms
Sulfapyridine sodium culture . . . . .	1,035 million organisms
Sulfathiazol culture . . . . .	960 million organisms
Sulfamethylthiazol culture . . . . .	580 million organisms

A comparison of the percentage inhibition of growth as determined by the photonreflectometer count (I) and by the manometric measuring of the oxygen consumption (II) shows the results obtained by the two methods in close agreement at this stage of the reaction of the brucella culture with the drugs.

	I.	II.
Sulfanilamide . . . . .	84.6	86.3
Sulfapyridine sodium . . . . .	92.0	91.8
Sulfathiazol . . . . .	92.6	92.4
Sulfamethylthiazol . . . . .	95.5	96.0

That means that at this stage of the experiment the oxidative metabolism of the brucella organisms is in no way affected by these drugs, but only the rate of growth. The growth-inhibiting effect on brucella, therefore, cannot be explained, as has been suggested (Long and Bliss<sup>3</sup>) by an indirect effect *via* inhibition of processes that sustain the energy supply of the bacteria, but must be interpreted as a direct effect of the drug on factors concerned with cellular multiplication. The first effect of these drugs is "sterilization" of the bacteria, which leaves their life-sustaining metabolic reactions unchanged.

Another effect of sulfamethylthiazol, however, besides this first effect of inhibiting bacterial growth, becomes apparent when the experiment is carried on over a longer period. This effect could not have been found with the density determinations alone without applying the cell physiologic methods. They show that, in contrast to the other drugs tested on this strain of brucella, sulfamethylthiazol not only inhibits the growth of the organisms much more effectively, but that, in addition, it causes a very marked decrease of their metabolism, as evidenced by the dropping of the rate of oxygen consumption per *unit* of bacteria.

Table 1 gives the results of an experiment with a m/40 phosphate pH 7.4 brucella broth culture of an initial density of 32 million organisms per cc. Each manometer vessel contained 2 cc. culture = 64 million organisms. Oxygen consumption and number of bacteria were measured after 24, 28, and 46 hours.

The figures show that not only the total amount of oxygen consumed and the absolute number of bacteria in the culture are smaller in sulfamethylthiazol than in sulfanilamide, but that also the ratio rate of oxygen consumption to unit of bacteria decreases

in sulfamethylthiazol with prolonged action of the drug on the culture. This ratio  $\frac{\text{c.mm. O}_2 \text{ consumed}}{100 \text{ million bacteria} \cdot \text{hour}}$  which in all the other cultures examined in this experiment varied between 1.65 and 1.38, is in sulfamethylthiazol after 46 hours only 0.41. The photonreflectometer count shows that between the 28th and 46th hour of the experiment, a comparatively slight but definite increase of the number of bacteria as such has taken place also in sulfamethylthiazol, the increase being 177%. The determination of the oxygen consumption does not only fail to show this increase, but reveals a decrease of 20% instead. This indicates that at this stage of the experiment, either all the bacteria that do grow under exposure to sulfamethylthiazol are impaired by 70% as to their metabolic activities, or that of the 1490 million organisms counted in the sulfamethylthiazol culture after 46 hours, only 450 million organisms are actively alive, whereas 1040 million organisms have ceased to carry out their life-sustaining chemical reactions and, from the point of view of bacterial physiology, must be considered dead.

TABLE 1.—EFFECT OF 5 MG. PER 100 CC. SULFANILAMIDE AND 5 MG. PER 100 CC. SULFAMETHYLTHIAZOL ON CELL COUNT AND METABOLISM OF 2 CC. OF A M/40 PHOSPHATE PH 7.4 BROTH CULTURE OF BRUCELLA MELITENSIS. INITIAL DENSITY: 32 MILLION ORGANISMS PER CC. 38° C. AIR.

Culture.	Hours after beginning of experiment.	C.mm. O <sub>2</sub> consumed per hour.	Number of bacteria. 100 million.	C.mm. O <sub>2</sub> consumed. 100 million bacteria · hour.
Drug-free . . . . .	24	181.5	120.0	1.51
	28	332.0	236.0	1.41
5 mg. per 100 cc. sulfanilamide .	24	22.0	14.0	1.57
	28	55.8	40.5	1.38
	46	684.0*	414.0	1.65
5 mg. per 100 cc. sulfamethylthiazol	24	6.4	4.35	1.47
	28	7.66	5.39	1.42
	46	6.1†	14.9	0.41

\* Measured after diluting with new broth.

† Measured both in original culture and after diluting with new broth.

Since the injurious effects of bacteria are coupled with their metabolic reactions, such a marked decrease in the metabolic reactions as found in the sulfamethylthiazol culture must lead to a corresponding decrease in the injurious effects on the host. Expressed in terms of practical therapeutics: sulfamethylthiazol not only, through its retarding action on the brucella growth, gives the body a better opportunity to avail itself of its own bactericidal power, but also, when allowed sufficient time for reaction, brings about direct qualitative changes causing irreversible damage to the individual bacteria.

Such gradual dying off of a brucella culture through prolonged action (86 hours) of sulfamethylthiazol is illustrated in Figure 2 by the decrease of the bacterial metabolic activity after a short initial period of increase, as revealed by the rate of oxygen consumption per hour of the culture.

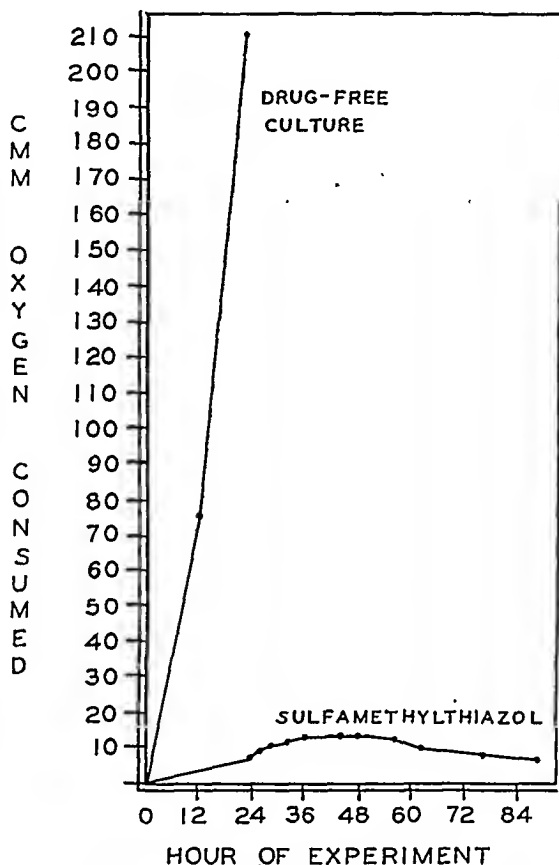


FIG. 2.—Effect of prolonged action of 5 mg. per 100 cc. sulfamethylthiazol on the rate of oxygen consumption per hour of 2 cc. broth culture *Brucella melitensis* (strain Huddleson).

Table 2 gives a comparison of the effect of various sulfanilamide drugs in concentrations of 5 mg. per 100 cc. on the brucella strain. We found the rate of oxygen consumption per hour after 29 hours, in the drug-free culture 185 times greater than at the beginning of the experiment, in promin 116 times greater, in benamide 95.6 times, in sulfanilamide 41 times, in sulfapyridine sodium 17 times, in sulfathiazol 11 times, in sodium disulon 6.4 times, in sulfamethylthiazol 3.8 times greater. That means, the inhibition as against the drug-free control was in promin of 44%, in benamide of 48%, in sulfanilamide of 78%, in sulfapyridine sodium of 91%, in sulfathiazol of 94%, in sodium disulon of 96.5%, in sulfamethylthiazol of 98%.

TABLE 2.—EFFECT OF EQUAL CONCENTRATIONS (5 MG. PER 100 CC.) OF VARIOUS SULFANILAMIDE COMPOUNDS ON CELL COUNT AND METABOLISM OF 2 CC. OF A M/28 PHOSPHATE PH 7.4 BROTH CULTURE OF *BRUCELLA MELITENSIS*. INITIAL DENSITY 40 MILLION ORGANISMS PER CC. 38° C.

Culture.	Hours after beginning of experiment.	C.mm. O <sub>2</sub> consumed per hour.	Number of bacteria, 100 million.	C.mm. O <sub>2</sub> consumed, 100 million organisms' hour.
Drug-free . . . . .	29	207.0	178	1.16
Promin . . . . .	29	129.5	155	0.835
Benamide . . . . .	29	107.0	94	1.14
Sulfanilamide . . . . .	29	45.8	36	1.27
Sulfapyridine sodium . .	29	19.0	153	1.08
	45	165.0		
Sulfathiazol . . . . .	29	12.3	15.4	0.8
Sodium disulon . . . . .	29	7.2		
	45	11.5		
	69	58.6		
Sulfamethylthiazol . .	29	4.3	13.2	0.26
	45	5.0		
	69	4.3		
	77	3.4		

After 45 hours the sulfapyridine sodium culture, as the table shows, has so to speak overcome the inhibition by the drug; activity and quantity of the culture are now about as high as they were in the drug-free control after 24 hours. The inhibiting effect of sodium disulon and sulfamethylthiazol is still undiminished after 45 hours; but 24 hours later, 69 hours from the beginning of the experiment, the inhibiting effect of sodium disulon too has been overcome by the bacteria, and only sulfamethylthiazol still displays its full inhibitory power. Even after 77 hours no increase of bacterial activity could be detected in the sulfamethylthiazol culture; on the contrary, the rate of oxygen consumption was definitely decreased, as compared to that found 24 hours after the beginning of the experiment.

**Summary.** The advantages of the cell physiologic manometric methods for the study of the effect of the sulfanilamide compounds on bacteria are discussed compared with the conventional bacteriologic methods of culturing and counting.

The effect of various sulfanilamide drugs on large inocula of Huddleson's strain of *Brucella melitensis* was examined by measuring manometrically with the Warburg method the oxygen consumption of the culture, and the density with the photorefractometer Libby. The drugs tested were: sulfanilamide, sulfapyridine sodium,

sulfathiazol, sulfamethylthiazol, sodium disulon, benamide and promin.

All these drugs were found to be effective in retarding growth in *Brucella melitensis*. The order of their effectiveness, in equal concentrations of 5 mg. per 100 cc. in broth cultures, after a period of 29 hours, for example, was: promin inhibited growth by 44%, benamide by 48%, sulfanilamide by 78%, sulfapyridine sodium by 91%, sulfathiazol by 94%, sodium disulon by 96.5% and sulfamethylthiazol by 98%.

The greater effectiveness of sulfamethylthiazol was evident within the first 12 hours of the experiment, when the oxygen consumption in the sulfamethylthiazol culture was only increased by 12%, as compared with an increase of 105 to 111% in sulfanilamide, sulfapyridine sodium, sulfathiazol and in the drug-free control. With longer duration of the drug action, the difference between the inhibitory effect of sulfamethylthiazol and that of the other sulfanilamide drugs became still more apparent. While even in sodium disulon, second to sulfamethylthiazol in effectiveness, the metabolism of the culture was 52 times greater after 69 hours than at the beginning of the experiment, in sulfamethylthiazol it was hardly 4 times as great.

It could be shown that sulfamethylthiazol in a concentration of 5 mg. per 100 cc., besides inhibiting growth, had a direct cell-damaging effect on the brucella strain examined.

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### PENETRATION OF BLOOD CLOT BY SULFANILAMIDE, SULFAPYRIDINE, SULFATHIAZOLE AND SULFA- METHYLTHIAZOLE.

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DURING a clinical study of the effect of certain recently developed chemotherapeutic compounds on the course of subacute bacterial endocarditis, it appeared desirable to investigate the ability of these

compounds to penetrate blood clot. It is a well established observation that in subacute bacterial endocarditis the organisms in the vegetations are separated from the blood stream only by a thin layer of fibrin. This barrier is, of course, partially broken down from time to time as vegetations break off or multiplying organisms erupt through the surface of the vegetation. However, as a rule, foci of organisms in the deeper layers of the thrombus remain to carry on the infection. If this were not the case spontaneous healing would be the rule instead of the rare exception, for the killing power of the serum bathing the vegetation is usually very high for the organisms located just beneath its surface. In order to understand the mode of action of drugs in subacute bacterial endocarditis it becomes important to know whether the drug can reach the organisms by penetrating the layer of fibrin which ordinarily protects them.

**Procedure.** Ten cubic centimeters of human blood was withdrawn, allowed to clot and remain clotted for 24 hours. Then 1 cc. of a solution of sulfapyridine was added to the serum and allowed to remain for another 24 hours. The clot was then removed and chemical determinations of the amount of sulfapyridine present were made on both the clot and the serum. The method used was that of Marshall and Bratton. The clot was prepared by washing thoroughly with 30 cc. of distilled water, drying on filter paper and then weighing. Next it was broken up with a stirring rod and boiled in distilled water three times. After each boiling the supernatant was filtered through Whatman No. 2 filter paper into a volumetric flask. When cool the contents were made up to volume with distilled water and a trichloroacetic acid filtrate of appropriate dilution prepared according to the method of Marshall and Bratton, the final determination being done on this filtrate. The serum in this experiment yielded 19.5 mg. per 100 cc., and the clot 0.3 mg. per 100 cc., sulfapyridine. The wash water yielded 0.07 mg. per 100 cc. sulfapyridine. In four subsequent determinations no sulfapyridine was found in the wash water and this procedure was therefore eliminated in later experiments.

Similar determinations were made after the clot had stood in sulfapyridine solutions for 24 hours, 5 days and 10 days (see Table 1). No appreciable penetration of the clot was observed under any of these circumstances.

TABLE 1.—RELATIVE CONCENTRATIONS OF VARIOUS DRUGS IN SOLUTIONS AND IN BLOOD CLOTS AFTER SUSPENSION FOR 24 HOURS, 5 DAYS AND 15 DAYS.

Drug.	Blood. (cc.).	Clot. (hrs.).	Time in sol. (hrs.).	Drug in sol. mg. per 100 cc.	Mg. of drug in clot.
Sulfapyridine . . . .	2	72	24	10.0	0
Sulfathiazole . . . .	2	48	24	16.3	0
Sulfamethylthiazole . .	2	48	24	17.2	0
Sulfanilamide . . . .	2	48	24	16.1	0.2
Sulfapyridine . . . .	2	72	120	10.0	0
Sulfathiazole . . . .	2	72	120	14.5	0
Sulfamethylthiazole . .	2	72	120	14.3	0
Sulfanilamide . . . .	2	72	120	23.6	0
Sulfapyridine . . . .	2	72	240	10.0	0
Sulfathiazole . . . .	2	72	360	17.1	0
Sulfamethylthiazole . .	2	72	360	18.0	0.2
Sulfanilamide. . . .	2	72	360	Hemolysis	Hemolysis

Blood clots were likewise suspended in solutions of sulfanilamide, sulfathiazole and sulfamethylthiazole for 24 hours, 5 days and 15 days. Again, no appreciable penetration of the clot was observed (Table 1).

A fibrin clot was prepared by centrifuging 10 cc. of freshly drawn blood at high speed. The superficial white clot which formed was removed after 72 hours and suspended in a solution of sulfapyridine for 24 hours. The solution yielded 27 mg. per 100 cc. sulfapyridine, the clot none (Table 2).

As a control 1 cc. of sulfapyridine solution was added to 10 cc. of freshly drawn blood which was then allowed to clot and remain clotted for 24 hours. Determinations on the serum yielded 11.8 mg. per 100 cc. sulfapyridine; on the clot 7.9 mg. per 100 cc. (Table 2). This is in accord with Finland's observation that sulfapyridine is distributed throughout the body water both intracellularly and extracellularly in approximately equal amounts.

No.	Blood.	Clot.	Time in S.P. sol.	S.P. in solution, mg. per 100 cc.	S.P. in clot, mg. per 100 cc.
1 . .	10 cc.	24 hrs.	24 hrs. (serum)	19.5 mg. 100 cc. serum	0.3
2 . .	Fibrin		24 hrs.	27	0
	10 cc.	72 hrs.			
3 . .	Sulfapyridine added before clotting		24 hrs. (serum)	11.8 mg. 100 cc. serum	7.9

TABLE 2.—SULFAPYRIDINE PENETRATION OF BLOOD CLOTS.

No. 1. Relative concentration of sulfapyridine in serum and blood clot after 24 hours' contact.

No. 2. Relative concentration of sulfapyridine in an acellular fibrin clot and in the solution in which it was suspended for 24 hours.

No. 3. Relative concentration of sulfapyridine in serum and in a blood clot when sulfapyridine was added before clotting occurred.

**Discussion.** These experiments afford an explanation for some of the apparent discrepancies between the bactericidal effect of sulfanilamide and allied compounds *in vitro* and their therapeutic effectiveness in subacute bacterial endocarditis. Even in those cases in which the drug is actively bactericidal for the causative organism, it is probably prevented from coming into contact with it by an impenetrable layer of fibrin. This does not mean, however, that complete eradication of the infection is theoretically impossible. In the course of time all of the preëxisting thrombi should become organized into fibrous scar tissue while all newly formed thrombi in a patient under active treatment will be impregnated with the drug. Thus conditions will tend to become less and less favorable for growth of the organism if an effective drug is taken continuously over a long period of time.

**Summary.** Human blood clots suspended in solutions of sulfanilamide, sulfapyridine, sulfathiazole and sulfamethylthiazole for periods of 24 hours to 15 days did not show any appreciable penetration by the drugs. The inferences to be drawn from these observations in relation to the chemotherapy of subacute bacterial endocarditis are discussed.

## THROMBOCYTOPENIC PURPURA DUE TO SULFAPYRIDINE.

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RECENT medical literature contains many reports of agranulocytosis and severe hemolytic anemia caused by sulfapyridine. There have been no reports of thrombocytopenic purpura caused by this drug. It seems worthwhile that 2 cases of this disease caused by sulfapyridine should be reported.

**Case Abstract.** CASE 1.\*—M. R., a negro, aged 41, developed chills and fever 4 days prior to admission to the hospital. On admission, the temperature was 104° F. Physical examination showed evidence of consolidation of the left lower lobe and a few râles in the left upper pulmonic area. Roentgen ray showed pneumonitis of the left lower lobe and a cavity in the left upper lobe. The day after admission, acid-fast bacilli were found in the sputum. No pneumococci were found. Another Roentgen ray 4 days later showed extension of the process in the left lung. During the first 10 days in the hospital he received 4.5 gm. of sulfapyridine daily (total dose of 45 gm.). Ten days after admission he developed hemoptysis and recurrent epistaxis. The drug was discontinued. On the eleventh day he developed a generalized purpura involving the entire body and the epistaxis and hemoptysis became continuous. He also developed oozing from the gums. On transfer to the Tuberculosis Service at Grasslands Hospital, he had generalized purpura, profuse bleeding from the mucous membranes of the mouth and nose with large adherent clots filling the mouth and nasal passages. The heart rate was 130, rhythm regular, no murmurs. There was dullness with increased vocal fremitus and resonance throughout the left chest. A record of the blood picture on admission and subsequently is given in Table 1. Included in this table also is a record of transfusions.

A diagnosis of thrombocytopenic purpura was made.

It was suggested that the patient receive multiple transfusions, intravenous vitamin C, 1000 mg. daily, local application of fer de lance venom to bleeding areas.

The day after admission he received 550 cc. of whole blood and the bleeding from the mucous membranes subsided. He continued to have purpuric manifestations for 5 days after the first transfusion. Ten weeks after receiving sulfapyridine he developed progressive jaundice without fever or pain. The feces remained highly colored. The area of liver dull-

\* Case "M. R." is presented through the courtesy of Dr. W. G. Childress, Physician in Charge, Division of Tuberculosis and Diseases of the Chest, Grasslands Hospital.



TABLE 1.—M. R.

Date.	R.B.C. (mill. per c.mm.).	W.B.C.	Hgb., Neweomer (%).	Differential leukocyte count.						Sputum.	N.P.N.	Trans- fusion (cc.).
				St.	Seg.	Lym.	Mono.	Eosin.	Bas.	Plat.		
12/10/39	3.74	6550	73	0	84	15	1	0	0	60,000		
12/11	3.01	6900	65	..	..	..	..	..	..	...	54.5	550
12/12	3.41	5050	56	19	56	15	10	0	0	34,000	..	600
12/16	3.78	..	71	..	..	..	..	..	..	123,000	Neg.	
12/19	2.74	8400	60	..	..	..	..	..	..	183,000	..	300
12/21	3.18	9350	68	..	..	..	..	..	..	178,000	+	300
12/26	4.08	6900	65	11	61	23	5	0	0	205,000	+	
1/7/40	4.10	8400	73	..	..	..	..	..	..	300,000	Icterus index	
2/4	4.50	7200	76	0	64	31	5	0	0	310,000	2/29/40	75
3/2	4.20	4800	76	..	..	..	..	..	..	311,000	Neg.	64
3/7	4.40	8200	82	18	56	24	0	2	0	501,000	Neg.	27
4/9	5.50	8000	90	16	60	20	4	0	0	....	Neg.	19

TABLE 2.—F. N.

Date (1940).	R.B.C. (mill. per c.mm.).	W.B.C.	Hgb., Neweomer (%).	Differential leukocyte count.						Hemato- crit.	Trans- fusion (cc.).	Bleed- ing time (min.).	Coagu- lation time (min.).
				St.	Seg.	Lym.	Mono.	Eosin.	Bas.	Plat.			
2/8	4.40	6,000	74	11	62	19	8	0	0	App. norm.			
2/18	3.89	7,650	64	..	..	..	..	..	..	7,780	500	17	7
2/19	4.26*	8,000	72	..	..	..	..	..	..	12,780			
2/20	3.34	5,050	53	17	59	16	5	2	1	...	600	21	7½
2/21	3.61	8,950	53	18	60	14	6	1	1	3,610	600	51	6
2/21	2.85	19,000	45	..	..	..	..	..	..	1,425	...	47	9
2/22	0.98		11	..	..	..	..	..	..	None seen	...	184	

ness appeared decreased by approximately 40%. He was given a high carbohydrate diet, 200 cc. of 25% glucose intravenously daily and 5 mg. of thiamin chloride orally three times a day. The curve of the icterus index indicates the rate at which the jaundice disappeared. As the jaundice subsided his appetite increased. Pneumothorax treatments were instituted and the tuberculous process which had involved both apices has shown marked regression.

Other laboratory tests performed were: Kline, negative; blood sulfapyridine on admission, 2.9 mg. per 100 cc.; serum albumin, 3.9; serum globulin, 2.7; total protein, 6.6; phosphorus, 4.1; phosphotase, 6.2 Bodansky units; galactose tolerance test showed results within the limits of normal; prothrombin clotting time 89% of normal.

CASE 2.—F. N. The patient was an Italian-born white man of 60. He had measles and whooping cough during childhood. The family history was without record of value. Three days prior to admission he developed a sore throat, fever, pain in the chest, dyspnea, and a non-productive cough. Physical examination revealed a well-nourished white male showing marked dyspnea. The throat was inflamed and there was mucopurulent exudate over the pharyngeal wall. Examination of the chest showed dullness with diminished breath sounds and moist râles at the base of the left lung. The heart was normal. The abdomen presented no abnormalities and neurologic examination showed nothing abnormal. The blood pressure was 120/80. Roentgen ray of the chest on the day of admission showed consolidation of the left base. A Roentgen ray diagnosis of lobar pneumonia was made. The temperature on admission was 103.2° F. and 4 hours later rose to 104° F. At that time he was given sulfapyridine and received 18 gm. in the next 4 days. The temperature dropped in 24 hours to 100.8° F. and on the fourth day was normal. The drug was discontinued on the fourth day because of hematuria. This was followed by a rise in temperature to 102.4° F. and during the next 3 days he received an additional 5 gm. of sulfapyridine. This caused a fall in temperature to 100° F. He received a total of 23 gm. of the drug.

Sputum typing showed no pneumococci Types I to XXXIII either by Neufeld reaction or mouse inoculation. Pneumococci of a higher type were present. Sputum culture showed a few pneumococci; 60% *Staph. albus* and 30% hemolytic streptococci. Throat culture showed 70% hemolytic staphylococci and 30% hemolytic streptococci. His blood picture is given in Table 2.

The urine after 4 gm. of sulfapyridine had been given showed albumin 1+; a few fine and coarse granular casts; 15 to 20 R.B.C. per high-power field.

Two days after admission a throat irrigation showed much mucous streaked with blood. Six days after admission another urinalysis showed 1+ albumin; occasional coarse granular casts; 40 to 50 R.B.C. per high-power field. Seven days after admission he developed epistaxis which lasted 6 hours despite energetic treatment. On the eighth day of hospitalization he developed purpuric manifestations in the skin of face and extremities. Recurrent bleeding from the nose continued. The next day he developed bleeding from the gums and mucous membranes of the mouth. Large ecchymotic areas appeared on the skin of extremities and trunk. Blood studies established a diagnosis of thrombocytopenic purpura and the results are recorded in Table 2.

The patient began to pass bulky tarry stools. The pulse became rapid and diffuse perspiration developed. The patient received three transfusions totalling 1700 cc. of whole blood with very little effect on the bleeding

tendency. He also received cevitamic acid, 150 mg. orally, daily; intravenous injections of oxalic acid 5 mg. twice daily without appreciable effect on the bleeding. On the day of his death, the bleeding time was 3 hours, 4 minutes and no blood platelets could be found in the stained smears. He died 14 days after admission. Autopsy could not be obtained.

Bone marrow biopsy showed the following differential:

Myeloid cells:	Per cent.
Undifferentiated cells . . . . .	1.0
Myeloblasts . . . . .	1.1
Premyelocytes:	
Neutrophils . . . . .	3.0
Eosinophils . . . . .	2.0
Basophils . . . . .	0.5
Myelocytes:	
Neutrophils . . . . .	9.1
Eosinophils . . . . .	6.3
Basophils . . . . .	1.1
Metamyelocytes:	
Neutrophils . . . . .	6.1
Eosinophils . . . . .	3.2
Basophils . . . . .	0.0
Segmented forms:	
Neutrophils . . . . .	3.1
Eosinophils . . . . .	2.8
Basophils . . . . .	0.0
	<hr/> 39.3
Erythroid cells:	
Megaloblasts . . . . .	3.4
Macronormoblasts . . . . .	33.2
Normoblasts . . . . .	18.5
Megakaryocytes . . . . .	3.5
Lymphocytes . . . . .	1.9
Plasma cells . . . . .	0.2
	<hr/> 60.7
	<hr/> 100.0

The only significant changes from normal in the cellular studies of the bone marrow are the moderate increase in megakaryocytes and a definite increase in the nucleated red blood cells. The increase in the latter is undoubtedly due to a response on the part of the bone marrow to the loss of blood.

**Conclusion.** Two cases of thrombocytopenic purpura developing during the course of treatment with sulfapyridine are reported. One case also showed evidence of acute toxic necrosis of the liver. The disease was fatal in 1 case. A bone marrow biopsy study in this case is reported.

It seems advisable that patients receiving sulfapyridine should be under close observation with frequent studies of the peripheral blood and frequent examinations of the urine. As soon as toxic manifestations develop the drug should be discontinued.

## POSTPUBERTAL MENORRHAGIA AND ITS POSSIBLE RELATIONS TO THROMBOCYTOPENIC PURPURA HEMORRHAGICA.

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THROMBOCYTOPENIC purpura hemorrhagica apparently of the idiopathic type may develop in association with menstrual disturbances, the circumstances being such as to suggest more than mere coincidence. It is now known that in the majority of women there is a physiologic decrease in the number of platelets in the circulating blood in the 2 weeks preceding menstruation, the low point being reached on the first menstrual day.<sup>11</sup> This helps to throw light on those interesting patients whom Minot described under the title of "Intermittent Menstrual Types of Purpura Hemorrhagica with Lymphocytosis."<sup>8</sup> The old observation that some women bruise more easily before their menstrual period seems to have a definite basis. Certainly menorrhagia may be the most important of a number of hemorrhagic phenomena caused by thrombocytopenia.<sup>4</sup> It is seldom realized, however, at least in this country, that severe menorrhagia may be the only symptom of essential thrombocytopenic purpura. Recent reports from various European clinics indicate that this occurrence is not altogether rare and that instances of serious or even fatal menstrual hemorrhage are likely to have such an origin.<sup>6,13</sup> Israel and Mendell<sup>6</sup> recently reported a case in which splenectomy was necessary to halt serious menorrhagia. C. T. Smith<sup>12</sup> also noted the importance of blood platelet counts in girls who at puberty show hemorrhagic tendencies; with menstrual hemorrhage an outstanding feature. We wish to report herein the development of idiopathic thrombocytopenic purpura in a young girl whose only symptom was severe menorrhagia. Splenectomy was curative. We have included abstracts of histories of: 1, another girl with menorrhagia of puberty with moderate thrombocytopenia; and 2, a woman who suffered from menorrhagia since puberty, developing in later years the complete clinical picture of essential thrombocytopenic purpura.\*

\* We are able to include this interesting case through the kindness of Dr. Thomas Klein of the Philadelphia General Hospital.

**Case Abstracts.** CASE 1.—H. T., a 14-year-old girl, was first admitted to the Jewish Hospital on June 9, 1939, on the service of Dr. Joseph Doane, and later studied by Dr. Mitchell Bernstein. The patient began to menstruate when 12½ years old. The first 6 periods occurred regularly on a 28-day cycle, each lasting 5 days. Thereafter, they were irregular, delayed once for 3 months, during which time a few spots, possibly purpuric, appeared in the skin of the knees and elbows. They disappeared in a few days. Otherwise, neither undue ecchymosis nor other hemorrhagic changes were ever noted. In June, 1939, shortly after the onset of an irregular menstrual period, profuse uterine hemorrhage began, which soon caused an acute anemia with marked pallor and weakness. On admission to the hospital the patient's erythrocyte count was 2,000,000 and the Hgb. 31%.

A total of 16 blood transfusions had to be given in almost daily sequence before the hemorrhage was definitely controlled. It did stop on June 22, but recurred on the 26th and continued profusely into the first week of July. The hemoglobin which had risen to 93% fell back to 43%. Following a brief respite, another hemorrhage of 4 days' duration occurred. It was not clear whether these recurrences were really menstrual periods. Before and in both of them large doses of progesterone, 5 mg. intramuscularly, were given almost daily. This, plus the daily administration of 200 rat units of antuitrin S for 7 days in conjunction with the numerous transfusions, finally controlled the hemorrhage. Which of these measures was responsible could not be determined. The patient was discharged on July 19th with the diagnosis of uterine hemorrhage due to progesterone deficiency, based on the report of Dr. S. Levine who in an endometrial biopsy noted "absence of progesterone activity." Numerous tests appeared to exclude at that time the possibility of a blood dyscrasia. The blood platelet count was 150,000, the bleeding and coagulation times were normal, each being 4 minutes.

The patient did not bleed at home for 3 weeks, although receiving no treatment. Prior to the onset of menstruation in August she received "prophylactically" 5 daily intramuscular injections, each 5 mg., of progesterone (proluton, corpus luteum extract). A profuse menstrual hemorrhage began, necessitating readmission to the hospital on August 24, on the service of Dr. Harold Goldburgh. At this time there was a mild fever, tachycardia and marked anemia. The erythrocyte count was 2,100,000 and the Hgb. 30%. In contrast with previous findings the bleeding time was greatly prolonged, being more than 20 minutes, and the platelet count was 2000. The coagulation time was 2½ minutes and the erythrocyte fragility zones were normal. Other laboratory tests were negative. The Rumple-Leeds test was negative despite the scarcity of blood platelets, the tourniquet being left on the arm for 10 minutes without the appearance of a single petechial mark.

There was nothing else of note in the examination. The girl was well developed and apparently free of any infection that could be relevant to the hemorrhagic state. A pelvic examination revealed no abnormality. Neither the superficial lymph nodes nor the spleen were palpable, although the latter was thought to be enlarged by percussion.

It was thought that endocrine dysfunction was the important cause of the menorrhagia and therapy was carried out accordingly. The patient received 1750 cc. of blood in 5 transfusions in the first week of hospitalization. Progesterone, 5 mg. per day, was given intramuscularly for 1 week and shortly afterward in 10 mg. doses each day for 9 days. Following this, we administered 30 mg. in 2 days without any beneficial effect on the bleeding then occurring, or on the low platelet counts. A little later progesterone was again given in 5 mg. doses almost daily for 22 days. Anterior pituitary-like hormone was used intermittently, finally in 2 cc. doses,

3 times per week for 1 month. Irradiation of the pituitary and of the ovaries was carried out as suggested by the gynecologic and radiologic consultants, but without any definite clinical effect. The local use of radium for metromenorrhagia was suggested as a palliative measure, but was rejected for various reasons.

The erythrocyte count was gradually elevated, apparently as a result of the many transfusions, so that on October 5 it was 5,000,000 with 90% hemoglobin. Nevertheless, the platelet count remained constantly low, coming up from the originally very low counts of 2000 and 3000 to a level of about 25,000. The uterine hemorrhage slackened but recurred with such frequency as to rule out at this time any dependence on a menstrual cycle. Very few days were free of hemorrhage and with the cessation of blood transfusions repeatedly sharp drops in hemoglobin occurred, threatening the development of a chronic anemia. Eventually, on October 16, the tourniquet test was positive, numerous purpuric spots appearing within 3 minutes; on October 21, purpura was noted on both legs.

On October 21, Dr. Edward Steinfield reported on a sternal bone marrow biopsy. He found adequate erythropoiesis and granulopoiesis. Normal maturation of those series was noted. No megakaryocytes were seen which, in view of the thrombocytopenia, was considered indicative of a depressed thrombocyte formation.

On October 25, splenectomy was performed by Dr. Frank Block. The spleen was not weighed, but it was moderately enlarged, measuring 10 by  $7\frac{1}{2}$  by  $3\frac{1}{2}$  cm. Dr. Levine later found changes indicative histologically of thrombocytopenic purpura.<sup>9</sup>

The result was decisive. The preoperative platelet count was 22,200. At noon, October 25, immediately after the operation, the count was 29,000; at 3 P.M. it was 45,000, and on the next day, *i. e.*, the first postoperative day, the count rose to 137,000. On November 1, it was 810,000, followed thereafter by a gradual decline to more normal figures. The bleeding time on the first postoperative day was reduced to  $4\frac{1}{2}$  minutes and on November 1 (the sixth postoperative day) it was  $1\frac{1}{2}$  minutes. Vaginal bleeding continued for 4 postoperative days, gradually diminishing, and then ceasing altogether. Endocrine therapy had been discontinued shortly before operation.

The patient was discharged on November 14, with normal blood findings and free of hemorrhage for 16 days.

"Follow up" examination revealed a normal blood status. The blood platelet count on April 10, 1940, was 360,000. Menstruation returned in December, 1939, but has not occurred since then, an amenorrhea of 4 months' duration. There is no evidence of any hemorrhagic tendency.

CASE 2.—K. McG., a 13-year-old white girl menstruated for the first time on May 29, 1937. After a moderate 2-day flow, the menstruation ceased, but returned 2 days later, from which time the patient bled continuously in increasing amounts. She was hospitalized on June 17, at which time she was extremely pale and moderately dyspneic. The hemoglobin was 31%, the erythrocyte count 2,000,000, blood platelets 110,000. The temperature was  $100.3^{\circ}$ , the pulse rate was 140, and hemic murmurs were heard over the precordium. The patient had previously been in excellent health, had not suffered from any hemorrhagic tendency. There was no history of self-medication. The diagnosis was "functional bleeding due to endocrine disturbance." The patient received 4 transfusions of 250 cc. each in 6 days. On June 23 the platelet count had risen slightly to 128,000. On June 24, menorrhagia stopped, and on June 28, the blood count showed a hemoglobin of 60%, 3,300,000 erythrocytes and 180,000 platelets. The only medication was the daily injection of 2 cc. antuitrin S for a period of 1 week.

The patient was discharged on July 7, 1937, apparently well. Menorrhagia has not recurred. It is of interest, however, that a younger sister, six years old, is now in the hospital with a complete picture of idiopathic thrombocytopenic purpura.

CASE 3.—B. P., a white woman, aged 51, complaining of "hemorrhages over the body," was admitted to the Philadelphia General Hospital on the medical service of Dr. Thomas Klein. She had noted excessive bleeding from small cuts for many years, especially in the last 2 years. In 1938 there was a serious hemorrhage from a tooth socket following dental extraction, and at that time she noted black and blue spots in the skin, appearing first on the legs and later over the entire body. In the last 3 months her body has been covered with recurring purpuric spots.

Her menstruation began at the age of 11. Menstrual bleeding from the beginning was excessive, continuing from 7 to 10 days, and usually so profuse as to confine her to bed for 2 to 3 days because of hemorrhage *per se*. Menorrhagia continued regularly until the age of 38 when menstruation suddenly ceased. On admission to the hospital, the erythrocyte count was 4,210,000, the leukocyte count 5400 and the Hgb. 85%. The blood platelet count was 120,000 and the bleeding time was 14 minutes.

This patient's daughter, aged 27, began to menstruate when 10½ years old. Her menstrual history is identical with that of her mother, featured by marked menorrhagia that has resisted medical treatment. There has been no history of purpura. Unfortunately, the platelet count and bleeding time have not been recorded.

**Discussion.** It is apparent that idiopathic thrombocytopenic purpura, at first "sans purpura," may occur at puberty or shortly thereafter in association with menstrual irregularities. Milder degrees of the menorrhagia of puberty relieved by blood transfusions as in our Case 2, or terminating spontaneously, are not uncommon. The basis of the association with menstruation remains obscure. In some patients a hemorrhagic tendency was noted in early childhood, reappearing at puberty with severe menorrhagia. Such patients are possibly like those of Minot, precipitated into clinical activity by premenstrual thrombocytopenia. The problem, however, of puberty or postpuberty thrombocytopenic purpura appears to be more complex. Some patients, as in Case 2, never showed a hemorrhagic tendency. Case 1, aside from a few possibly purpuric spots recalled only after persistent questioning, likewise was in excellent health until the advent of menorrhagia. Detailed blood study in this case did not reveal at first any change suggestive of thrombocytopenic purpura. One month later with the recurrence of menorrhagia, the platelets had practically disappeared from the circulating blood and the bleeding time was greatly prolonged. In Case 2 severe hemorrhage continued for 3 weeks; the platelet count was low, 110,000, a level, however, somewhat higher than the severity of the symptoms would suggest if the diagnosis of uncomplicated essential thrombocytopenic purpura was correct. Similarly with Israel and Mendell,<sup>5</sup> the patient had been bleeding for 3 weeks, at which time the platelet count was 190,000, the bleeding time 7 minutes. While the latter was moderately prolonged, the data were not indicative of thrombocytopenic purpura and it was

only after further examination revealed progressive blood changes that the diagnosis could be made. It is clear then that severe menorrhagia at puberty may precede and actually initiate the clinical state of idiopathic thrombocytopenic purpura. One may postulate a "qualitative" deficiency of the platelets which, however, will not explain normal or only slightly prolonged bleeding times in initial examinations. Factors aside from splenic dysfunction may be important. It has been suggested that a relationship exists between the spleen and the female endocrine system, especially that part of it governing menstruation, in which the thrombolytic action of the spleen may be unduly stimulated.<sup>10</sup> It is conceivable that a toxic effect leading to destruction of blood platelets or megakaryocytes may be traced to some abnormality in the complicated menstrual cycle.

An experimental Werlhof disease has been produced in dogs by injection of various sex hormones,<sup>1</sup> but this thrombolytic effect has never been demonstrated in human beings.<sup>2,14</sup> Charlotte Ehrenberg<sup>3</sup> injected large doses of corpus luteum extract into 2 dogs and observed definite qualitative and quantitative platelet deficiencies within 24 hours. This supported Ehrenberg's belief that corpus luteum therapy may aggravate menorrhagia, as it did in her patient. Unaware of this work, we also felt that corpus luteum was possibly a factor in these cases because its development in the last 2 weeks of the menstrual cycle coincides with the usual reduction in blood platelets. Gynecologic consultants had recommended its use in Case 1 to prevent recurring menstrual hemorrhage. Accordingly, the patient received large injections of progesterone (proluton) on the last 5 premenstrual days. The expected protective action was entirely missing. The patient had to be promptly rehospitalized and at this time the platelet count was 2000. Six daily transfusions finally brought the hemorrhage under partial control, but while the erythrocyte count rose from 2.1 million to 3.5 million and the Hgb. from 30% to 60%, the platelets remained at a low level of 3500, as evidenced by daily counts. The usual postmenstrual rise in platelets did not occur. During this time, the patient received 5 mg. of progesterone every day. Corpus luteum therapy was clearly ineffective and exerted if anything a deleterious effect.

There was, on the other hand, no doubt of the existence in this case of idiopathic thrombocytopenic purpura. While for many weeks menorrhagia was the only hemorrhagic sign, the full picture of purpura, impaired capillary resistance and positive laboratory signs eventually became evident and the results of splenectomy confirmed the diagnosis. This gradual unfolding of the clinical picture may be emphasized as characteristic of puberty thrombocytopenic purpura. The evolution may be delayed for a long time. In the series of cases of Leschke and Wittkower,<sup>7</sup> depicting various types of thrombocytopenic purpura, there is (Case 6) the interesting



example of "monosymptomatic" involvement, a woman aged 23 who since her first menstrual period at the age of 11 suffered severe menorrhagia requiring repeated hospitalization. Purpura did not appear for many years despite the fact that nose bleeding and unduly large bruise marks were noted for a brief time in early childhood. The platelet count, first determined at the age of 22, was 3700. Instead of splenectomy, the surgeon removed the uterus and a cystic degenerated right ovary. Not only was there cessation of menorrhagia, but the nosebleeds noted preoperatively disappeared, notwithstanding the fact that the blood platelet count remained constantly under 3000 and the bleeding time 45 minutes. After 2 postoperative years of apparently restored health, purpura appeared for the first time and impaired capillary permeability was noted. One may speculate on the possibility in such a case of a stimulation of splenic thrombocytolytic activity by a factor inherent in an abnormal menstrual cycle, the stimulation remaining years after surgical removal of the inciting factor. Some of these patients have structural changes associated with menstruation. Case 1 showed a "progesterone" deficiency in endometrial biopsy. The patient of Israel and Mendell had an "atrophic and dysplastic" endometrium.

Finally, a familial tendency to thrombopenia is apparent in some cases. Case 2 is suggestive and in Case 3, while the data remain incomplete, the history is indicative of an inherited tendency. Other cases of serious thrombopenic menstrual hemorrhage almost certainly show this familial trait.<sup>14</sup>

**Summary.** There is a small group of girls, apparently in otherwise good health, who at the onset of puberty or soon afterwards develop menorrhagia associated usually with irregularities in cycle.

This menorrhagia may be the first indication of idiopathic thrombocytopenic purpura. The deficiency in blood platelets and the increased bleeding time pathognomonic of this disturbance may gradually appear after a variable length of time. Similarly, the appearance of impaired capillary resistance and of spontaneous purpura is delayed for many weeks or months. The medical history may reveal a past hemorrhagic tendency in early childhood which apparently disappeared only to return at puberty as an abrupt and serious menorrhagia.

Splenectomy is curative as far as the hemorrhagic process is concerned, and is indicated in those cases where repeated blood transfusions and endocrine therapy have failed to check the hemorrhagic tendency and the fall in platelet count.

It is suggested that some abnormality in the menstrual cycle may stimulate the thrombocytolytic activity of the spleen. The exact nature of this interrelationship requires further elucidation. Corpus luteum may be a factor as indicated by its destructive effect

on the blood platelets in experimental work. There is some slight clinical evidence of this effect in patients of the type herein described.

The blood platelets should be counted and the bleeding time determined in every case of menorrhagia in adolescent girls. These tests should be repeated despite initial normal findings if the hemorrhagic process continues.

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## ACUTE NEPHRITIS: REVIEW OF 77 CASES.\*

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THE conception of acute glomerular nephritis as a disease of children which follows severe infections, especially scarlet fever, and is characterized by albuminuria, hematuria, edema, and convulsions has been shown to be inadequate. Due in large measure to the studies of Löhlein,<sup>19</sup> Addis,<sup>1</sup> and Longcope,<sup>20a</sup> its relation to other infections, particularly streptococcal infections of the upper respiratory tract, has been appreciated, and it has become more and more apparent that the renal lesion is only one, albeit usually the most conspicuous one, of the manifestations of the reaction to infection which is called acute nephritis.

While acute nephritis is more common in children than in adults, it may occur at any age. Moreover, not only is the prognosis more serious in the older age groups, but the onset is frequently more insidious and the symptoms less dramatic. The greater number of reports on the symptoms and particularly the prognosis of acute nephritis have been concerned with children. Within the past few years, several reports on the disease in adolescents and adults have appeared. These have emphasized the frequency of apparently mild

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infections of the upper respiratory tract as the precursors of acute nephritis and the high incidence of the subsequent development of chronic nephritis.

This report describes the symptoms and clinical course of 77 cases of acute glomerular nephritis treated in Lakeside Hospital from 1931 to 1939. Table 1 shows the age distribution, sex, color, and incidence per 1000 admissions. The proportion of colored patients (19%) is approximately that of hospital admissions. On the other hand, 81% of the cases of acute nephritis were in males, while they comprise only 43% of admissions. The material is not representative of the incidence of acute nephritis for several reasons. Only the severer cases of acute nephritis were admitted to the wards. The few children included are those admitted to the surgical wards, as these were the only records of children admitted to the University Hospitals that were available for study.

TABLE 1.—YEARLY ADMISSIONS, AGE AND SEX DISTRIBUTION OF 77 CASES OF ACUTE NEPHRITIS.

Year.	Number.	Rate per 1000 admissions.	Age.	Number.
1931 . . . . .	2	0.23	0-10	6
1932 . . . . .	7	0.73	11-20	22
1933 . . . . .	10	1.11	21-30	23
1934 . . . . .	8	0.79	31-40	11
1935 . . . . .	8	0.71	41-50	12
1936 . . . . .	5	0.40	51-60	1
1937 . . . . .	10	0.77	61-70	1
1938 . . . . .	15	1.10	71-80	1
1939 . . . . .	12	0.84		
Total . . . . .	77			

Male white, 43; colored, 12. Female white, 19; colored, 3.

A history of a preceding infection was obtained in 75 of the 77 cases. Of these, infection of the upper respiratory tract, sinuses, and ears accounted for 56. These etiologic factors are shown in Table 2 where a number of similar studies on adults have been assembled from the recent literature for comparison. Scarlet fever may be regarded as an infection of the upper respiratory tract, and if so grouped, infections of the upper respiratory tract account for 669 (69%) of the collected cases. The incidence of acute nephritis in these infections is, however, low. Kayser-Petersen and Schwab<sup>12</sup> found only 10 instances of acute nephritis in 479 cases of angina. The reported incidence after scarlet fever has varied in different epidemics, from about 5% in McCrae's<sup>22</sup> series to 1.3% in that of Lucchesi and Bowman.<sup>21</sup> Scarlet fever is apparently much less likely to be followed by glomerulonephritis in adults than in children. While the incidence of nephritis following upper respiratory tract infections is thus quite low, the complication may have such serious consequences that its early recognition is of the utmost importance.

The incidence of pneumococcic pneumonia preceding nephritis differs considerably in different reports. Some authors do not report

any cases, while according to others it accounts for 5% to 8% of the cases. Of course, febrile albuminuria is common in pneumonia; a few red cells, particularly in the urine of bacteremic patients, not uncommon. Such findings are probably indicative of a focal nephritis, the result of localized infection in the kidney rather than the allergic response which is recognized as acute diffuse glomerulonephritis. Seegal<sup>30</sup> reported 7 instances of acute nephritis in 1004 cases of pneumonia. Goldring and Wyckoff<sup>9</sup> found 2 patients who developed typical glomerulonephritis, with hematuria, edema, and elevated blood pressure among 44 cases of lobar pneumonia whose kidney function was carefully followed. In these cases, symptoms developed 12 and 13 days after the crisis.

TABLE 2.—PRECEDING INFECTION IN ACUTE NEPHRITIS.

	Murphy and Rastetter. <sup>28</sup>	Leavell <i>et al.</i> <sup>11</sup>	Falkers. <sup>8</sup>	Longcope. <sup>20</sup>	Richter. <sup>27</sup>	Seegal. <sup>31</sup>	Volhard. <sup>13</sup>	Lichwitz. <sup>18</sup>	Hayman and Martin.	Total.	Per cent.
Number of cases . . . . .	150	82	68	116	100	218	71	94	77	976	
Sore throat, tonsillitis . . . . .	21	21	0	68	37	94	17	28	27	313	32.1
Upper respiratory tract . . . . .	99	10	31	0	27	37	8	9	17	238	24.4
Otitis and sinusitis . . . . .	0	4	0	21	2	17	0	0	12	56	5.7
Scarlet fever . . . . .	2	8	6	9	4	9	19	3	2	62	6.4
Skin infections . . . . .	0	5	5	8	0	0	0	19	3	40	4.1
Pneumonia . . . . .	0	0	0	0	5	15	6	4	9	39	4.0
Rheumatic fever . . . . .	1	0	0	4	1	7	2	0	2	17	1.7
Miscellaneous . . . . .	21	17	6	1	9	22	17	5	3	101	10.3
Infection unknown . . . . .	6	17	20	5	15	17	2	26	2	110	11.3

Another disease in which the relation to acute nephritis is uncertain is rheumatic fever. While during the febrile stage there is an increased elimination of protein, casts and cells, true glomerular nephritis is certainly uncommon. Bachr and Schiffrin<sup>3</sup> found only 3 instances among 235 autopsied cases of rheumatic fever dying during the acute stage, and of these they believed one antedated the rheumatic infection and another was terminal. Loeb<sup>18</sup> and Goldring,<sup>8</sup> however, have reported typical cases, and it was present in 4.7% of cases of rheumatic fever observed by Salvesen.<sup>29</sup> The common microscopic hematuria in rheumatic fever is probably an expression of the hemorrhagic tendency of the disease rather than of glomerular inflammation. The urinary changes must be accompanied by edema or hypertension before a diagnosis of acute glomerulonephritis is justified.

In subacute bacterial endocarditis, in addition to the focal embolic lesion, diffuse glomerulonephritis is not uncommon, while in the

atypical verrucous endocarditis of Libman and Sacks it is almost constant.

Cultures from the nose and throat or suspected focus of infection were made in 62 cases. The results are shown in Table 3. Although these cultures were made in the routine laboratory, and it is quite possible that a higher incidence of hemolytic streptococci might have been found by special techniques, this organism was the predominant one in at least 44% of the cases. This is only about half its incidence in Longcope's cases. Rake<sup>26</sup> gives an even higher percentage, stating that "99 per cent of cases of nephritis follow a streptococcal infection." In each of the cases of acute nephritis in this series associated with dermatitis, hemolytic streptococci were recovered from the skin lesions, in 2 in pure culture. Goodwin<sup>11</sup> has commented that impetigo contagiosa is often the only discoverable infection preceding nephritis in children.

TABLE 3.—ORGANISMS RECOVERED IN CULTURES FROM THROAT, SINUS, OR SKIN.

Organism.	No. of cases.
<i>Streptococcus hemolyticus</i> . . . . .	27
<i>Streptococcus viridans</i> . . . . .	9
<i>Streptococci hemolyticus</i> and <i>viridans</i> . . . . .	7
Streptococci, unclassified . . . . .	4
Pneumococci, Type I, II, XIV . . . . .	5
Pneumococci, untyped . . . . .	5
Staphylococci only . . . . .	5

The interval between the onset of the preceding infection and the first symptoms of nephritis is difficult to determine with any accuracy. Many patients were admitted with well developed symptoms; indeed, often when symptoms were already subsiding, and were unable to tell when these had first appeared. A still greater number were unable to give exact dates for the preceding cold or sore throat. From the data on the records the interval was less than 1 week in 5, from 1 to 2 weeks in 29, from 2 to 3 weeks in 18, 4 weeks in 9, and 5 weeks in 3 cases. In 9 instances no record of the interval was made and in 4 it was so vague as to be meaningless.

The cardinal symptoms of acute nephritis are hematuria, edema, and hypertension. Yet as Murphy and Rastetter<sup>25</sup> pointed out, if the presence of all three is required for a diagnosis many mild cases will be overlooked, and not until years later when chronic nephritis is obvious will the significance of the mild early episode be apparent. The incidence of the more common symptoms are given in Table 4.

The urinary syndrome is the most important, because it is not only the most constant but is usually essential for the diagnosis. In 1 case anuric from admission to death the diagnosis was apparent from history, edema, hypertension, and nitrogen retention, and was confirmed at autopsy. In 1 other patient the initial urine was recorded as showing many red cells, but no albumin; subsequent specimens contained both. In all the other cases the urine contained

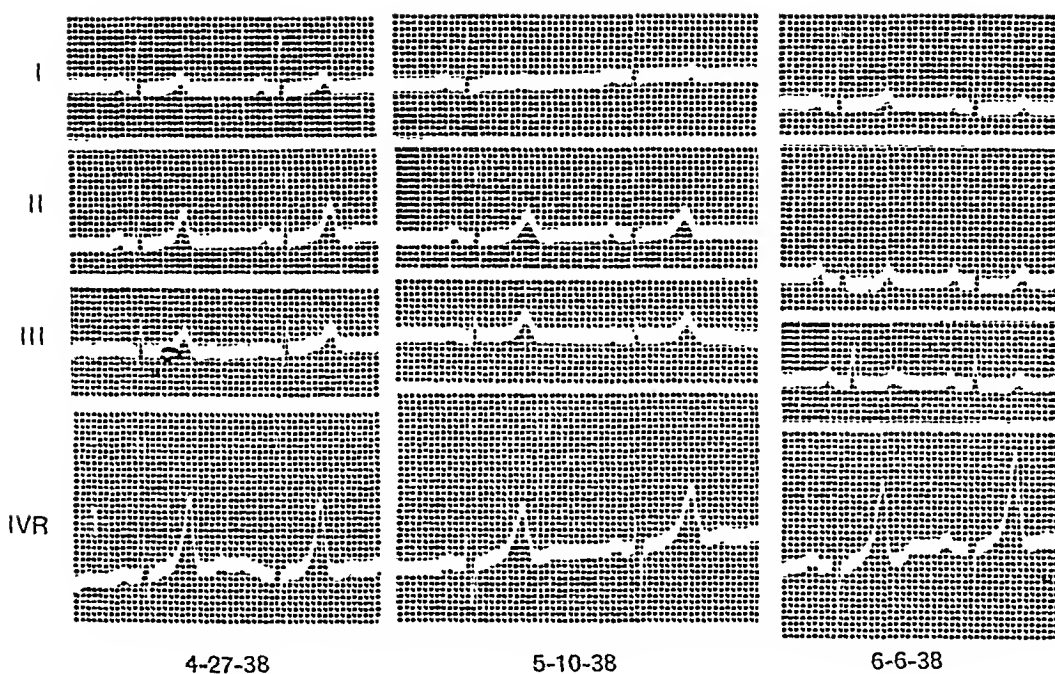


FIG. 1.—Electrocardiographic changes during the course of acute nephritis. On admission, April 27, 1938, *T* waves tall and peaked in Leads 2, 3, and 4R; *Q-T* prolonged. May 10, 1938: *T* smaller in amplitude; *T* less peaked in Leads 2, 3, and 4R; *Q-T* prolonged. June 6, 1938: Normal record; *Q-T* prolonged.



both albumin and an abnormal number of red cells. Albuminuria alone is indicative of a renal lesion, but is not sufficient to justify a diagnosis of nephritis. The so-called febrile albuminuria occurs at the height of fever or infection and disappears as the temperature reaches normal. It is probably not due so much to the fever *per se* as to a temporary increase in glomerular permeability brought about by circulating toxic substances, for a similar albuminuria occurs in various afebrile toxemias and chemical poisonings. In the 20 cases in which it was recorded in this series the amount of protein varied from less than 1 gm. to 14 gm. a day; in 10 (one-half) it was less than 2 gm. Frequently there were wide fluctuations in the amount of albumin excreted from day to day. The amount of proteinuria did not bear any relation to the severity of the attack nor to the outcome. Bell<sup>4</sup> has shown that the amount of albumin need not correspond to the degree of glomerular damage, for those glomeruli most severely affected have closed capillaries and hence do not transmit albumin.

TABLE 4.—SYMPTOMS IN 77 CASES OF ACUTE NEPHRITIS.

Hematuria . . . . .	76*
Albuminuria . . . . .	75*
Casts . . . . .	61
Hypertension—Systolic above 140 . . . . .	54
Diastolic above 90 . . . . .	49
Edema—Face . . . . .	45
Legs . . . . .	30
Pulmonary râles . . . . .	18
Pleural effusion . . . . .	7
Ascites . . . . .	6
Nitrogen retention . . . . .	33
Uremia (BUN above 90) . . . . .	7
Convulsions . . . . .	3
Vomiting . . . . .	3

\* One patient anuric from admission to death.

The degree of hematuria also varies; 31 patients had gross hematuria, in the remainder it was apparent only on microscopic examination.

The urine volume in acute nephritis is usually said to be reduced and the specific gravity high. This is in keeping with the pathologic picture of swollen, ischemic glomeruli and relatively intact tubule cells. There is a reduced renal blood flow, diminished volume of glomerular filtrate, but efficient tubular concentrating power. However, many of these patients showed specific gravities below 1.020. This raised the question among the house staff and students whether the patient did not have an exacerbation of a chronic rather than an acute nephritis. The specific gravity was recorded in 73 cases; of the 37 in which it was below 1.020, 22 were obviously losing edema at the time of admission as evidenced by a large urine volume and loss of weight. Five others were very mild cases and had been treated by forcing fluids. The remaining 10 are of particular interest. The



24-hour urine volume ranged from 220 cc. to 800 cc., averaging 340 cc. The specific gravity in one was 1.017, in the others 1.012 to 1.014. A small volume of dilute urine betokens impairment of tubular function, and therefore more extensive renal damage than is usually present. This was borne out in these cases: of the 10, 2 died in the hospital, 4 have gone on to chronic nephritis, and only 4 have recovered from the acute nephritis.

Systolic pressures above 140 mm. Hg were present in 54 cases (70%) and in 49 (64%) the diastolic was above 90 mm. Hg. The degree of elevation of blood pressure did not bear any relation to the severity of the attack nor to the outcome. Pressures of 210/150 may drop to normal in a couple of weeks, while hypertension may be absent throughout, and yet the patient go on to the development of chronic nephritis. Persistent hypertension, however, represents an unhealed renal lesion, and a rising blood pressure, even if other signs of acute nephritis have disappeared, is an unfavorable omen.

The hypertension was attributed by Volhard<sup>33</sup> to arteriolar spasm. It certainly is not due to increased blood volume. Goldblatt's demonstration that renal ischemia leads to persistent hypertension, and the pathologic and physiologic evidence that renal blood flow in acute nephritis is reduced makes it seem highly probable that this mechanism is responsible for the hypertension.

Edema was noted in 45 cases (59%). It was most frequently noted in the face, next about the ankles. Pulmonary râles, unassociated with obvious pulmonary infection, were recorded in 18 patients (23%). Pleural effusion was present in 7, and demonstrable ascites in 6. It must be pointed out that the criteria for edema on physical examination are very crude, and that a patient may have considerable edema before this impresses the examiner. Thirty-seven patients were weighed on admission and at frequent intervals; 6 of these lost from 1.5 kg. to 7.5 kg., average 3.7 kg. with the onset of diuresis, and yet no edema had been recognized. In those in whom edema had been recorded the loss in weight was from 0.3 kg. to 16.0 kg., average 7.1 kg.

As long ago as 1879 Goodhart<sup>10</sup> called attention to the occurrence of cardiac failure in the early stages of acute nephritis. At first regarded as a rarity, the incidence of demonstrable cardiac involvement has risen with the more careful studies in recent years. Whitehall, Longcope, and Williams<sup>34</sup> found some degree of cardiac failure as shown by dilatation of the ventricles in 17% of mild cases of acute nephritis and in 89.8% of severe cases. In the severer cases there is dyspnea, orthopnea, elevated venous pressure, and the condition may readily be mistaken for acute heart failure. In addition, many cases show alterations in the electrocardiogram, most readily detected in serial records. The cause of these evidences of cardiac involvement is not entirely clear. Alwens and Moog<sup>2</sup> suggested that the increased size of the heart in teleoroentgenograms was due to

pericardial effusion. But the persistence of the enlargement after edema has disappeared and arterial and venous pressure have returned to normal makes this unlikely. That the hypertension is not the sole cause is indicated by the lack of correlation between blood pressure and cardiac enlargement, and its occurrence in the absence of significant hypertension (Levy<sup>15</sup>) or even of any hypertension at all. Rubin and Rapoport<sup>28</sup> believe that there is myocardial damage from infection, and Whitehall, Longcope and Williams believe the cardiac damage is intimately associated with the pathogenesis of acute nephritis, and an expression of the widespread capillary damage which occurs. The perivascular lesions and the acute arteriolitis reported by Stone,<sup>32</sup> and Feller and Hurevitz<sup>7</sup> in biopsies from the deltoid muscle and at autopsy in 2 cases of acute nephritis support this conception. Moreover, the electrocardiographic changes reported by Levy,<sup>15</sup> Master, Jaffee, and Dack,<sup>24</sup> Langendorf and Pick,<sup>13</sup> and others are indicative of myocardial damage rather than mechanical factors or pericardial effusion. These consist in abnormalities of the *T* wave, low amplitude, and prolongation of auriculoventricular conduction.

Only 9 patients in this series had repeated teleoroentgenograms. Of these 5 (56%) showed a significant decrease in cardiac diameter with recovery. Electrocardiograms were made on 27 patients; of these 12 (44%) were regarded as normal records, while 15 (56%) showed some abnormalities.\* Of the 12 patients showing normal tracings, 11 had only 1 record. In the 15 patients showing abnormalities, a single tracing was made in 8 instances, and two or more in 7. In the latter group, abnormalities were at times present in only one record. The abnormalities in the records consisted in alterations in the *T* wave, changes in amplitude of *QRS*, prolonged *P-R* interval, and changes in the *P* wave. These are detailed in Table 5. Thus, about half of the cases in which suitable studies were made showed evidence of myocardial damage.

TABLE 5.—ELECTROCARDIOGRAPHIC FINDINGS IN 27 CASES OF ACUTE NEPHRITIS.

Normal record . . . . .	13	<i>T</i> tall and peaked in I . . . . .	6
Small <i>P</i> wave . . . . .	3	II . . . . .	8
<i>P-R</i> of 0.2 sec. or more . . . . .	3	III . . . . .	3
<i>P-R</i> segment depressed . . . . .	1	IV . . . . .	3
Abnormal left axis deviation . . . . .	1	<i>T</i> negative in I . . . . .	1
<i>QRS</i> voltage decreased . . . . .	6	II . . . . .	2
<i>S-T</i> segment elevated . . . . .	1	III . . . . .	1
depressed . . . . .	1	<i>T</i> of Pardee type in I . . . . .	3
<i>T</i> diphasic in II . . . . .	1	II . . . . .	3
IV . . . . .	2	III . . . . .	1
		IV . . . . .	2

Thirty-three patients showed some nitrogen retention, taking 20 mg. per 100 cc. of urea nitrogen as the upper limit of normal. In the majority, however, the degree of retention was slight, 20 to

\* We are indebted to Dr. Harold Feil for interpreting these records.

40 mg. per 100 cc. of blood. Seven, however, had definite uremia with blood urea nitrogen above 90; of these, 4 died. Of the other 3, 2 were in the group mentioned above who passed only a small volume of dilute urine.

Convulsions occurred in only 4 cases. Two of these were in the uremic group with one death. In the other 2, the blood urea nitrogen was 31 and 40 mg. per 100 cc. One of these died immediately after a violent convulsion; the other, in whom the spasms were very mild, recovered. Nausea and vomiting were infrequent, in only 3 severe enough to be troublesome. Six patients complained of severe headache.

Of the 77 patients, 10 died in the hospital; of these 3 deaths were apparently due to the primary disease, leaving 7 (9%) attributable to acute nephritis. Of these 4 died in uremia with marked nitrogen retention, 1 of acute cardiac failure with pulmonary edema, 1 immediately after a generalized convulsion, and 1 eight hours after admission of uncertain cause. The diagnoses were confirmed at autopsy in 9.

TABLE 6.—PROGNOSIS IN ACUTE NEPHRITIS.

	No. of cases.	Died of acute nephritis.		No. Followed,	Interval, yrs.	Cured, %.	Latent, %.	Chronic, %.	Died of nephritis, %.
		No.	%.						
Murphy and Rastetter <sup>25</sup>	150	12	8.0	127	2-14	58.3	..	41.7	
McPhee and Kaye <sup>23</sup>	90	5	5.6	48	4-7	85.4	..	14.6	
Richter <sup>27</sup>	100	5	5.0	77	Av. 8	80.5	..	15.5	4.0
Longcope <sup>20b</sup>	141	7	5.0	134	½-14	42.5	32.0	11.2	14.2
Falkers <sup>6</sup>	68	6	8.8	41	?	56.0	..	19.6	24.4
Leavell <i>et al.</i> <sup>14</sup>	82	?	..	26	1-10	77.0	19.2	3.8	
Hayman and Martin	77	7	9.1	52	½-10	67.3	17.3	9.6	5.8

Of the 67 who left the hospital, 12 were apparently cured at that time, with no edema, normal blood pressure, and normal urine. Seven of this group have been followed and all remained well. Fifty-two patients have been followed for from 6 months to 8 years, average 2.4 years. The status is shown in Table 6. Those are recorded as well who are free from symptoms, have a normal blood pressure, no albumin or red cells in the urine according to clinical methods. In 11 urea clearance tests were normal (75% or above) and in 19 specific gravities ( $20^{\circ}/4^{\circ}$ ) of 1.020 or more gave added evidence of normal renal function. Some in the latent group, who have but recently had the acute attack will undoubtedly eventually recover. In this group are included those who have no symptoms and a normal urine, but a persistent systolic blood pressure above 140 mm. Hg (4 cases), and those who with a normal blood pressure continue to show albumin (5 cases), or albumin and red cells in their

urine. Those who have both elevated blood pressure and abnormal urine have been classed as chronic nephritis. The distribution agrees with that in other series which are shown for comparison.

All of the patients in this series who are classed as cured have shown a normal urine and blood pressure within 1 year after the acute attack, the majority within 6 months. Addis says healing occurs in the first year in 75% of those who recover and that there is no record of healing after 5 years. Since there is so little that can be done for the patient with chronic nephritis, this emphasizes the need for every effort to promote healing in the acute attack. What is the outlook for the patient who has recovered from acute glomerulonephritis? Is he more resistant or more susceptible? Although it is generally accepted that once healed acute nephritis does not recur, there is little in the literature to support this impression. Longcope reported 4 cases out of a series of 24 healed acute nephritis who subsequently showed hemolytic streptococci in one or more throat cultures without urinary abnormalities, and Loeb *et al.*<sup>17</sup> have recently described 10 patients who had been observed through an initial attack of acute nephritis, through a healed period, and through a subsequent infection with hemolytic streptococci without developing another bout of acute nephritis. On the other hand, Boyle *et al.*<sup>5</sup> reported 2 children who had had two distinct attacks of nephritis, each followed by complete recovery, and Richter<sup>27</sup> mentions one. We have as yet not seen a patient with two clear cut attacks of acute glomerulonephritis.

**Summary.** Of 77 cases of acute glomerular nephritis, 75% followed infection of the upper respiratory tract. While the disease occurs at all ages, it is most common before 30. The cardinal symptoms of hematuria, hypertension, and edema were not all present in every case. Evidence of cardiac involvement was present in approximately half the cases subjected to adequate study. Ten patients died in the hospital, 7 (9%) primarily of acute nephritis. Fifty-two of the remaining 67 patients were followed for 6 months to 8 years. Of these 35 (67.3%) are well, 9 (17.3%) have persistent albuminuria or hypertension, while 3 have died in uremia since discharge from the hospital, and 5 have chronic glomerular nephritis.

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## THE MOTOR REACTION OF THE DOG'S COLON TO INTRAVENOUS INJECTIONS OF *E. COLI COMMUNIOR*, *SPIRILLUM RUBRUM* AND *STAPHYLOCOCCUS AUREUS*.

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THE toxic effects of dead colon bacilli or fractions thereof have been discussed by various investigators. Such effects are mainly referable to the gastro-intestinal,<sup>1</sup> pulmonary<sup>3,8</sup> cardiovascular,<sup>3</sup> and central nervous systems<sup>7</sup>; and to temperature regulation.<sup>8</sup> Ecker and Biskind<sup>1</sup> in a series of observations on laparotomized dogs with the spinal columns crushed in the lower thoracic region reported no visible effects from intravenous injections of filtrates of *E. coli communior* on intestinal movements. On the other hand diarrhea, vomiting and tenesmus have been reported to follow intravenous injections of the dead bodies of this organism.<sup>7</sup> The work of Vaughan<sup>8</sup> and of Wheeler<sup>9</sup> indicates that the toxic substance associated with *E. coli communior* is intracellular and therefore would not be expected to be found in such filtrates as those used by Ecker and Biskind. The rapidity with which the toxic substance becomes active following intravenous injection of the whole dead organism is shown by the work of Templeton, Ferguson and Pilot,<sup>7</sup>

who reported gastro-intestinal upsets within 10 minutes, and a general depression within  $1\frac{1}{2}$  hours.

In a preliminary report Galapeaux, Adler, Ferguson and Templeton<sup>2</sup> called attention to a marked depression in colon activity, retching, vomiting and defecation resulting from intravenous injections of colon bacillus vaccines. They also pointed out that the activity of the colon was increased immediately prior to a defecation. This work has been subsequently extended to include studies on 5 dogs.

The animals used were cecostomized several weeks prior to this study and were trained to lie quietly on a cushioned table in the presence of ordinary noises and other disturbances encountered in the laboratory. The motility of the colon was recorded by two tandem balloon<sup>4</sup> systems as previously described.<sup>5,6</sup> Each tandem system consisted of three balloons, 3 cm. in diameter and 3 cm. in length, arranged in linear order and separated from each other by a distance of 3 cm. One system of balloons was inserted by way of the cecostomy for recording proximal colon motility and one system inserted through the anus to record distal motility. Each balloon was connected to a water manometer by way of a T tube. After the insertion of the systems, the balloons were alternately inflated and deflated a number of times to smooth out their contours, after which 6 cm. of water pressure was drawn against them for the purpose of standard deflation. Eight centimeters of water pressure was raised in each manometer and continuity between them and the deflated balloons was then established. By this method simultaneous records were obtained from six segments of the colon.

The colon bacillus vaccine used in this study was prepared from a stock culture kept on artificial media in the Loyola laboratories for the past 8 years. Nutrient agar was used as the medium on which the organisms for the vaccines were grown. After 48 hours of growth in coli flasks the organisms were washed with tap water into bottles and sterilized at a temperature of 56° C. for 30 minutes. Tests for sterility were made by plating on nutrient agar. The stock vaccines made from these cultures contained 6 to 9 million organisms per c.mm. Dilutions for injections were made at the time of use.

Before injections of the vaccines were begun, 21 control experiments of 400 minutes' duration were made on the animals used, in which no injections or interruptions occurred in the course of the experiment. The tracings thus obtained were then divided into 8 periods of 50 minutes each. The quantity of activity was calculated by considering only the time during which the gut was active. To accomplish this, two rules were rigidly followed. First, a segment of the colon was considered active if a contraction or contractions lasted for 1 or more minutes; and second, a period of quiet was considered to exist if no activity appeared in a segment for 2 minutes. The quantity of motility thus calculated in terms of percentage revealed an average activity varying between 59 to 66%.

The average activity recorded in each of the last four periods of the control tracings showed an approximate equal tendency to be above or below the average activity per 50 minutes of the first 200 minutes of the experiment.

Tracings of the same duration and under the same conditions were obtained from the animals used in the control study in which after a 200-minute control period 1 cc. of a diluted vaccine was injected intravenously. The vaccine injected was prepared from the stock solution previously described by diluting with sterile tap water in 1 to 7 proportion. From a series of 46 experiments, each having a control period of 200 minutes, following which the vaccine was injected, and 20 experiments in which no vaccine was injected, a

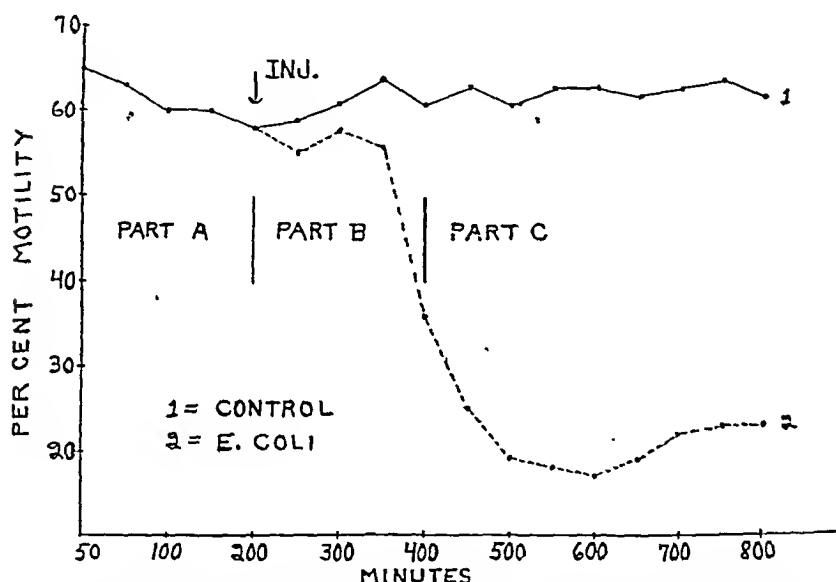


FIG. 1.—Ordinate — per cent of colon motility calculated in minutes. Abscissa — duration of experiment. Unbroken line — control motility. Broken line — motility after vaccine injection.

total of 66 experiments were obtained, each having a 200-minute control period (see Fig. 1, Part A). The activity of this control period varied from 56 to 64% the higher activity being in the first part of the experiments. During the second 200 minutes (Fig. 1, Part B), the control activity based upon 20 experiments during which no injections were made, varied from 59 to 64%. In those experiments in which the vaccines were injected at the close of a 200-minute control period, the activity was decreased below that of the controls throughout the succeeding periods of study. The activity of the first 50 minutes following the injection was somewhat depressed. This depression in turn was followed during the next 50 minutes by a slight rise in activity, although the percentage did not reach that of the control experiments. The duration of these

experiments, although adequate to show a marked depression in the last 50-minute period (between 150 and 200 minutes after the injection) was not sufficiently long to reveal the duration of this depression.

By another method of tabulation the relation of the quantity of activity of each 50-minute period following the injection was compared to the average quantity of activity of the four 50-minute periods preceding the injection. This method of compilation revealed that out of 46 experiments, only 26% showed activity in the first 50 minutes after injection to be above the average activity of the 200 minutes preceding the injection, thus supporting the compilation previously made which suggested a depression in colon activity during the first 50 minutes following the injection. In the succeeding two 50-minute periods, the opportunities for the activity to be above or below that of the average in the control periods seemed to be about equal; 56 and 52% of the experiments in the second and third periods respectively revealed activity above that of the average in the control periods. The most significant change in activity (Fig. 1) was seen between 150 and 200 minutes after the injection. This was marked by a depression in activity from approximately 56 to 35%. It is also significant that 81% of the experiments revealed a depression at this time.

Since no evidence of a return to normal activity was seen in the experiments of 400 minutes' duration, the necessity for longer experiments was obvious. For controls, 10 records were continued for an additional 400 minutes. In parallel, 19 experiments each with a 200-minute control period were followed for 600 minutes after the injection. The most significant depression of activity which occurred between 150 and 200 minutes, as previously described, was found to continue for approximately 4 hours. A slow return towards the normal was usually evident before the close of the experiment, and a complete return of normal activity was established within 16 hours at which time further control tracings were obtained. During the last 400 minutes 95 to 100% of all the experiments (Fig. 1) revealed a decrease in activity below that of the average activity in the control periods.

During the course of an experiment the reactions of the animals were carefully observed. About 30 minutes after the injection, an increase in salivation and some restlessness was commonly seen. Thirty to 40 minutes later, vomiting or defecation, or both, was frequent. These latter reactions continued at intervals for several hours. Just prior to a defecation there was an increase in the quantity of activity involving the colon as a whole. Following defecation there was usually a decrease in the quantity of activity.

Although the balloon method of recording is designed primarily for recording circular activity, in a few instances we observed a shortening of the colon to such an extent that longitudinal activity



must have made some impression on the balloons. In 4 instances during the period of defecation the distal balloon set was expelled and the distal balloon of the proximal set was also expelled through the anus. Since the proximal set was not free to move, being anchored at its entrance into the gut, the extrusion of its distal balloon through the anus must have been accomplished by a marked shortening of the longitudinal musculature. This mechanism may be of great importance in transporting fluid material of the proximal segments into the distal colon and may account in part for the further observation that at the termination of experiments the defecation which followed were of diarrheal consistency.

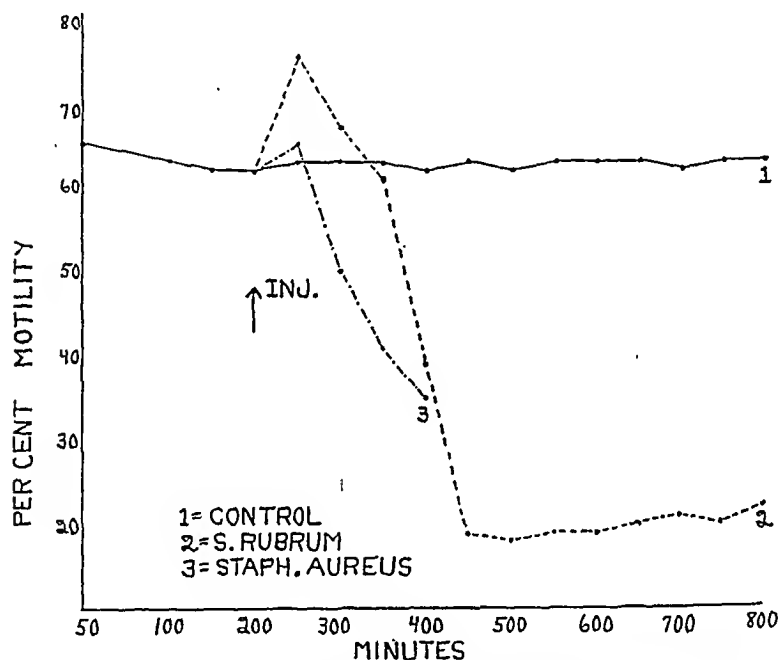


FIG. 2.—Ordinate — per cent of colon motility calculated in minutes.  
Abscissa — duration of experiment.

At times following an injection of *E. coli* vaccine, the animals ejected fluid material through the anus by violent contractions of the abdominal muscles, unassociated with activity of the colon which was recordable by the technique used in this study. The urinations observed in this study were usually initiated by vigorous abdominal contractions. In view of the profound reaction elicited by the dead bodies of *E. coli communior* on colon activity when injected intravenously, this study was extended to include two other organisms, *Spirillum rubrum* and *Staph. aureus*, which ordinarily exhibit a low toxicity. The vaccines of these organisms were prepared in the same manner as that of *E. coli communior*. Two of the

same animals were used and the same technique employed as previously described in this article.

In this study of the effects of intravenous injections of *S. rubrum* and *Staph. aureus* vaccines on colon motility, 52 experiments were conducted. In all cases the first 200 minutes were considered as a control period in which no experimental variations were introduced. At the close of this period intravenous injections of 4 cc. of a stock vaccine of *S. rubrum* containing 12 million organisms per c.mm. were given in 28 experiments, 20 of which were terminated at the close of 200 minutes and 8 continued for 600 minutes after the injection. In 11 experiments 4 cc. of a stock vaccine of *Staph. aureus* containing 12,200,000 organisms per c.mm. were given intravenously at the close of the 200-minute control period and continued for 200 minutes. Thirteen of the experiments were continued for 800 minutes without experimental intervention for controls. During the 200-minute control period the average number of the minutes of activity in 52 charts (Fig. 2) was found to vary from 65 to 68%. The average activity in the control experiments for the next 600 minutes varied from 64 to 70%. The most significant effect relative to motility was a decrease in the activity about 100 to 150 minutes after the injections, which was observed in the case of *S. rubrum* to become more profound during the next 200 minutes and to last for several hours.

All studies on *Staph. aureus* were terminated 200 minutes after the injection; however, the depression had reached a very significant level before the close of the experiments.

Although the number of organisms per c.mm. injected was much greater than that used in the study of *E. coli communior*, the general reaction of the animal was much the same. Nausea as indicated by increased salivation and movements of the jaws, vomiting and defecation were common occurrences.

**Summary.** 1. A slight depression in colon activity was observed during the first 50 minutes following the intravenous injection of *E. coli communior*.

2. The average activity per 50-minute period was somewhat increased between 50 and 150 minutes after an intravenous injection of *E. coli vaccine*.

3. Between 150 and 200 minutes after an intravenous injection of *E. coli vaccine* a profound depression began which persisted for several hours following which there was a slow return to normal.

4. Twenty-four hours after an intravenous injection of *E. coli vaccine* the quantity of colon activity had returned to normal.

5. An increase in the quantity of colon activity was observed immediately preceding the act of defecation elicited by an intravenous injection of *E. coli*.

6. Following the intravenous injection of *E. coli vaccine* all animals displayed signs of a general reaction to the vaccine such as

salivation, restlessness, periodic increased respiration and heart rate, abdominal distress indicated by a periodic hypertonicity of the abdominal muscles, vomiting, defecation and occasionally urination.

7. Occasionally, following the intravenous injection of *E. coli* vaccine, fluid material was expelled from the colon at the time of violent contractions of the abdominal muscles unassociated with a demonstrable colon activity.

8. The most significant result following intravenous injection of *S. rubrum* and *Staph. aureus* was a depression of colon motility becoming profound 150 to 200 minutes after injection.

The authors are indebted to Dr. A. J. Carlson, who made this study possible.

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## AN EVALUATION OF THE BRUCELLA OPSONOCYTOPHAGIC TEST.

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AMONG the laboratory procedures employed as diagnostic aids in suspected cases of brucellosis, the opsonocytophagic test has been used extensively. It is the purpose of this paper to examine the limitations and usefulness of this test. The data reported here have been accumulated from studies carried out on hospital patients, medical students, and members of the staff of Duke Hospital.

**Method.** The technique of the opsonocytophagic test as outlined by Huddleson<sup>4</sup> has been followed. A laboratory strain of *Brucella melitensis* var. *suis* obtained from Huddleson and an encapsulated strain of *Brucella melitensis* var. *suis*, isolated from a patient having Hodgkin's disease, have been used for the bacterial suspensions. The latter strain was used because this strain and others, isolated from patients having Hodgkin's disease, have been found to differ significantly from the laboratory strains.<sup>5</sup> The bacterial suspensions have been standardized by means of the photron-reflectometer to a density of 3 billion organisms per cc. Whenever intradermal tests with Brucellergin were made, the determination of the opsonocytophagic index and the agglutinin titer of the patient's serum has always been carried out before the skin test. The opsonocytophagic index number has been calculated by the method of Foshay and Le Blanc.<sup>3</sup>

*Normal Range of the Brucella Opsonocytophagic Index.* We have scrutinized our data very closely to determine the usual range of phagocytosis of *Brucella* organisms by the neutrophils of normal individuals, and have carried out simultaneous determinations of the opsonocytophagic index for *Eberthella typhosa*, *Salmonella suispestifer*, and *Proteus vulgaris*, using the same technique, in order to determine the usual range of phagocytosis of these organisms. The following table gives the range of the great majority of opsonocytophagic indices in normal individuals.

TABLE 1.—RANGE OF THE BRUCELLA OPSONOCYTOPHAGIC INDEX AND INDEX NUMBER IN NORMAL INDIVIDUALS.

	No. of bacteria ingested per neutrophils.				Opsonocytophagic index number.
	0.	1-20.	21-40.	41+.	
Lowest limit of normal range . . .	25	0	0	0	0
Usual upper limit of normal range . .	0	25	0	0	25

In any series, however, a few indices will be found such as 3-20-2-0. Because these minor variations in the index are not infrequent, we consider an index number of 30 to represent the upper limit of normal phagocytosis, and within this range falls the phagocytosis of the three organisms studied for purposes of comparison with *Brucella*. We do not distinguish between "negative" and "weak" phagocytosis as does Evans,<sup>1</sup> although her range for those, from an index number of 1 to 20 and from 21 to 30 respectively, corresponds with our range of normal or "negative" phagocytosis.

*Specificity of the Brucella Opsonocytophagic Index.* The question of the specificity of the *Brucella* opsonocytophagic index was raised early in this study. To determine whether the neutrophils of individuals phagocytosing *Brucella* organisms in high degree would phagocytose other organisms, simultaneous tests were made with a given blood sample using equivalent suspensions of *Eberthella typhosa*, *Salmonella suispestifer*, and *Proteus vulgaris*. The individuals used for this purpose were patients proven to be suffering from *Brucella* infection by the isolation of the organism, and healthy individuals having high degrees of phagocytosis for *Brucella* organisms. The results of this study are presented in Table 2, and show that in no instance was there significant phagocytosis of any of the other three organisms.

TABLE 2.—SPECIFICITY OF THE BRUCELLA OPSONOCYTOPHAGIC TEST.

Case . . . . .	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
	Opsonocytophagic Index Numbers*																							
<i>Brucella melitensis</i> var. <i>suis</i> (non-encapsulated)	81	52	90	89	56	45	47	63	39	0	39	41	40	81	60	45	60	48	36	47	67	94	59	
<i>Brucella melitensis</i> var. <i>suis</i> (encapsulated)										39	37	5	27	70	23	39	29	2	10	15	7	35	50	
<i>Eberthella typhosa</i> . . . . .	18	5	12	0	6	19	15	23	29	0	0	10	27	29	29	24	2	4	29	22	3	0	17	
<i>Salmonella suispestifer</i> . . . . .	22	9	17	3	5	29	5	21	20	5	15	5	3	5	13	5	9	8	6	29	0	10	11	
<i>Proteus vulgaris</i> . . . . .					0	1	18	0	27	12	2	13	0	3	0	27	0	6	0	22	10	3	15	4

*Comparison of the Opsonocytophagic Index With Different Brucella Strains.* The finding that many *Brucella* organisms isolated from patients having Hodgkin's disease are encapsulated, and differ significantly from the usual laboratory strains, led to a comparison of the opsonocytophagic indices, using equivalent bacterial suspensions of a non-encapsulated laboratory strain and of an encapsulated strain. Distinct differences in the degrees of phagocytosis have been found in many instances, which indicates the desirability of carrying out such determinations with both encapsulated and non-encapsulated strains. Similar differences have been found in the agglutination reactions using the two strains. Table 3 gives the results of such opsonocytophagic index determinations in 105 individuals.

TABLE 3.—DIFFERENCES IN THE OPSONOCYTOPHAGIC INDEX WITH NON-ENCAPSULATED AND ENCAPSULATED BRUCELLA STRAINS IN 105 INDIVIDUALS.

	Opsonocytophagic Index No.				
	0-30.	31-40.	41-60.	61-80.	81-100
Non-encapsulated strain . . . . .	95	22	17	5	1
Encapsulated strain . . . . .	95	13	6	3	0

Forty-one of the 105 individuals studied had positive *Brucella* opsonocytophagic indices. Of these, 28 indices were positive with the laboratory strain alone; 6 with the encapsulated strain alone; 7 with both strains.

*Comparison of the Brucella Opsonocytophagic Test With the Agglutination and Allergic Skin Test.* Close comparison of the results of intradermal tests with Brucellergin, agglutination reactions, and opsonocytophagic index determinations shows that the latter yields by far the greatest percentage of positive reactors. From the study of groups of patients suffering from a variety of diseases, and of normal individuals, the opsonocytophagic test has, apparently, a distinct usefulness in attempting to survey the incidence of contact with *Brucella* organisms in groups of individuals. The following table illustrates our findings.

TABLE 4.—SUMMARY OF LABORATORY TEST FINDINGS IN DIFFERENT GROUPS OF INDIVIDUALS.

	No. of individuals studied.	Positive Brucellergin intradermal tests, %.	Positive <i>Brucella</i> agglutinations, %.	Positive <i>Brucella</i> opsonocytophagic indices, %.
New Haven Hosp. patients† . . . . .	96	6.2	55.1	72.9
Duke Univ. School of Medicine students . . . . .	50	10.0	22.0	40.0
Duke Hosp. patients, Series I* . . . . .	196	11.1	19.3	39.2
Duke Hosp. patients, Series II* . . . . .	105	..	28.5	37.1

\* In Series I, the *Brucella* opsonocytophagic index and agglutination reactions were determined only for a standard laboratory strain. In Series II, both this non-encapsulated laboratory strain and an encapsulated *Brucella* strain were used.

† I wish to thank Dr. F. G. Blake and Dr. A. W. Oughterson for the privilege of using the data on these patients.

**Discussion.** On the basis of the degree of phagocytosis of *Brucella* organisms by an individual's neutrophils, several systems of classification and interpretation of the opsonocytophagic index have been made.<sup>1,4</sup> Huddleson's interpretation, requiring also the allergic skin test, has attracted particular attention and the limitations and inconsistencies of this system have been pointed out by several investigators.<sup>2,5</sup> On the basis of our experience we think that a positive *Brucella* opsonocytophagic index indicates only that a given individual has had contact with *Brucella* organisms, and reveals nothing as to the activity of *Brucella* infection. This point of view is confirmed by the finding of positive degrees of phagocytosis in healthy individuals, with no clinical history to suggest previous *Brucella* infection, and in individuals given killed *Brucella* organisms by the subcutaneous route. A negative *Brucella* opsonocytophagocytic index does not exclude contact or infection with *Brucella* organisms. In cases of proven brucellosis, and of *Brucella* infection coexisting with Hodgkin's disease, any significant degree of phagocytosis is frequently entirely lacking during active phases of the disease, and particularly when bacteremia is present. Similarly, opsonocytophagic indices repeated over a period of several months may show quite variable results. The effect of previous injections of Brucellergin, Brucellin, or *Brucella* vaccines upon the opsonocytophagic index, as well as upon the agglutination reaction, is well known and is mentioned only for emphasis. In no way is the opsonocytophagic test diagnostic of active *Brucella* infection.

**Summary and Conclusions.** 1. The usual range of the *Brucella* opsonocytophagic index in normal individuals, as expressed by the index number, is from 0 to 30.

2. A positive *Brucella* opsonocytophagic index is specific, that is, the individual's blood that is positive for *Brucella* does not phagocyte other organisms to any considerable degree.

3. A significant difference in the phagocytosis of non-encapsulated and encapsulated strains of *Brucella* organisms exists, and should be considered when this test is carried out.

4. The *Brucella* opsonocytophagic index has its greatest usefulness in indicating contact with *Brucella* organisms and, of the usual laboratory tests, is the single most useful test for survey work.

5. The *Brucella* opsonocytophagic index is not diagnostic of active *Brucella* infection and may be negative even when active infection exists.

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## INTUBATION STUDIES OF THE HUMAN SMALL INTESTINE.

## XIII. THE CONCENTRATION AND MOVEMENT OF GLUCOSE SOLUTIONS IN THE STOMACH AND DUODENUM.\*†

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It is probable that when a reasonable quantity of glucose is ingested it passes down the alimentary canal in progressively diminishing amount until all of it is absorbed. The amount and rate of absorption vary from mouth to anus and depend, in part, on the concentration of the solution and on the duration of contact with the mucosa in each area. Previous studies have shown, however, that, irrespective of the solution ingested, a concentration above 5% or 6% is rarely observed in the jejunum or ileum and that when stronger solutions are placed directly in the small intestine the processes of dilution, absorption and dispersion of the fluid along the gut reduce the concentration to a low level within a very few minutes. From this dilute solution the intestine can nevertheless withdraw the glucose at a rate unexplainable by simple osmotic diffusion and in amounts proportional to the concentration.<sup>1a</sup>

Implied by these observations are certain points concerning the behavior of the glucose prior to its reaching the jejunum, and it is the purpose of this and the two subsequent papers to consider the changes that take place in the ingested glucose solutions while still on the proximal side of the duodeno-jejunal junction. This report deals, 1, with the question of whether or not an initial delay occurs following the taking of a hypertonic solution before it begins to traverse the duodenum; 2, with the proportion of the total amount of glucose ingested that reaches the duodeno-jejunal junction; and 3, with the gradient of concentration throughout the stomach and duodenum during the period of gastric emptying. Preliminary reports on this work have already appeared.<sup>1a,b,5</sup>

I. Is the onset of gastric emptying delayed when a hypertonic glucose solution is ingested?

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*Method.* Normal adult human subjects were carefully selected for these experiments. To determine visually the appearance time of glucose in the duodenum and jejunum after the administration of a markedly hypertonic solution, barium sulphate was added to a 50% solution and the mixture swallowed by 11 normal individuals. Each subject was instantly placed in the prone position on the fluoroscopic table and the time of passage of the barium sulphate-glucose mixture observed.

*Results.* Table 1 shows that in most instances the opaque mixture was visible in the duodenum within 2 minutes or less after its administration.

TABLE 1.—GASTRIC AND DUODENAL EMPTYING TIME—FLUOROSCOPIC OBSERVATIONS.  
(Ingestion of 100 cc. 50% glucose plus BaSO<sub>4</sub>.)

No. of cases.	Enters duodenum.	No. of cases.	Enters jejunum (min.).
4 . . . . .	0-10 sec.	4 . . . . .	1
4 . . . . .	10-30 sec.	4 . . . . .	1-5
2 . . . . .	1-2 min.	1 . . . . .	12
1 . . . . .	30 min.	1 . . . . .	34
		1 . . . . .	52

Ages, 20 to 28 years. Heights, 5 ft. 1 in. to 6 ft. 2 in. Weights, 112 to 165 pounds.

*Discussion.* The results agree with the statement of Pendergrass<sup>9</sup> that there is no appreciable delay in the admission of a concentrated glucose solution into the jejunum. The poor initial recoveries from the duodenum after highly concentrated test meals, as shown in Chart 1, might in the absence of the roentgenologic evidence be interpreted as indicating a delay in the onset of gastric emptying, but more probably it is due to the rapid absorption of the first ejections before dilution has greatly increased the volume.

## II. What proportion of the ingested glucose reaches the jejunum?

*Method.* A complete collection of all the intestinal contents reaching the duodeno-jejunal junction after a test meal of glucose was made by applying constant suction to the gut lumen at that point. An obstructing balloon mounted on a second lumen of the same tube and just beyond the point of suction was kept distended in the upper jejunum. As the aspiration apparatus under working conditions has a withdrawal capacity of 150 cc. of intestinal contents per minute, we believe that no leakage past the balloon occurred. Glucose was taken by mouth or injected into the stomach through a separate tube after the withdrawal of fasting specimens. In the short experiments the stomach and duodenum were quickly emptied and washed through separate tubes. In the experiments which were carried on until practically all of the ingested glucose was absorbed the gastric and duodenal residue was withdrawn by the same tube that had been used during the experimental period for duodeno-jejunal aspiration. In either case the speed of emptying and washing was sufficiently great to give a satisfactorily clean-cut absorption time.



Considering the glucose from the duodeno-jejunal junction as that fraction of total amount ingested which would have been absorbed in the jejunum and ileum, one may then determine the ratio of gastro-duodenal to jejuno-ileal absorption.

### GLUCOSE CONCENTRATIONS

SIMULTANEOUS SAMPLES RECOVERED FROM STOMACH AND DUODENUM

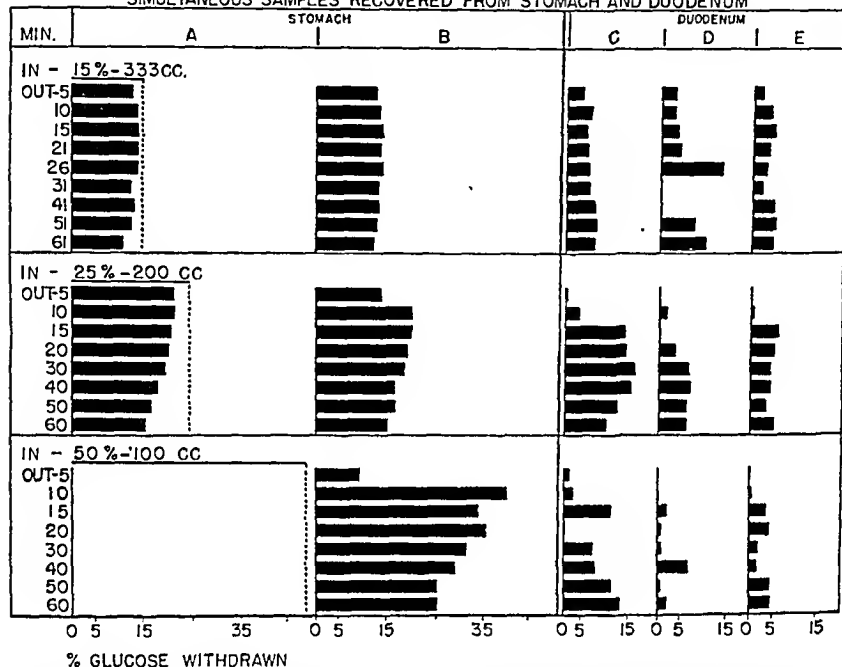


CHART 1.—The results of three experiments selected to contrast the effect on duodenal concentrations of the ingestion of widely different volumes and concentrations of glucose.

The samples were analyzed by the method of Benedict after filtrates were prepared according to Somogyi as reported in a previous paper.<sup>6</sup>

**Results.** Twenty-five experiments were performed (Table 2) in which the amounts of glucose ingested varied from 25 to 150 gm., the volume from 25 to 500 cc. and the concentrations from 5 to 50%. The duration of the experiments varied from 30 minutes to 4 hours. In 2 instances, only, was as much glucose recovered from the duodeno-jejunal junction as was absorbed in the stomach and duodenum, and in some instances essentially no glucose was obtained from this point. The amount leaving the duodenum was rather independent of the amount ingested and exceeded 9.6 gm. only in 3 instances.

**Discussion.** When glucose is ingested, even in large amounts, only a few grams of it reach the jejunum. This must mean an extraordinary power of absorption on the part of the duodenum or

a participation by the stomach in the absorption of glucose, particularly from highly concentrated solutions. As the first step in determining what the actual power of these portions of the digestive tube is with regard to absorption, it becomes important to know the concentrations actually occurring while absorption is normally in progress.

TABLE 2.—THE RATIO OF ABSORPTION ABOVE AND BELOW THE DUODENO-JEJUNAL JUNCTION.

Case No.	In stomach.		Absorbed above D.-J. junction.	Recovered from D.-J. junction.	Ratio.
	%.	Gm.			
215 . . . . .	5	25	18.0	6.9	2.6
149B . . . . .	20	40	11.2	0.3	37.0
145 . . . . .	25	50	47.4	2.6	18.0
146 . . . . .	25	50	30.8	19.2	1.6
151 . . . . .	25	75	40.7	0.0	
211 . . . . .	50	25	23.7	1.8	13.0
219 . . . . .	50	25	22.3	2.7	8.3
203 . . . . .	5	25	23.0	0.8	29.0
148A . . . . .	15	30	17.9	5.8	3.1
149A . . . . .	15	30	9.5	1.4	6.8
207 . . . . .	50	24	21.5	1.3	17.0
220 . . . . .	50	25	21.5	3.5	6.1
147A . . . . .	15	30	23.4	1.3	18.0
159 . . . . .	25	75	20.3	7.7	2.7
156 . . . . .	33	100	25.6	7.3	3.5
157 . . . . .	20	100	19.0	1.1	17.0
150 . . . . .	25	75	34.2	1.2	28.0
152 . . . . .	25	75	12.5	2.6	4.8
155 . . . . .	33	100	16.9	9.6	1.8
161 . . . . .	25	75	18.4	7.9	2.4
162 . . . . .	25	75	11.9	13.0	0.9
154 . . . . .	33	100	87.9	2.2	40.0
163 . . . . .	5.4	27	12.3	6.8	1.8
160 . . . . .	50	150	12.9	14.4	0.9
158 . . . . .	25	75	26.6	0.3	
212 . . . . .	50	25	..	0.1	

NOTE.—The variations in the quantities absorbed are in large part due to variations in the lengths of the experiments.

III. At what concentrations may glucose be recovered from selected points in the stomach and duodenum?

*Method.* By the use of a 2- and of a 3-lumened tube, perforated at appropriate points and inserted at the same time, five samples of contents from predetermined areas of the stomach and duodenum were recovered at practically simultaneous time intervals after the ingestion of a hypertonic glucose solution. The points in the digestive tract which were sampled are indicated in Figure 1. The position of the tubes was confirmed by fluoroscopy every 5 minutes without moving the subject. Care was also taken to maintain him in a uniform position, to avoid his swallowing saliva and to prevent nausea and gagging. Analyses of the samples, therefore,

gave data for the determination of the gradient of glucose concentration for any given moment from the body of the stomach to the beginning of the jejunum. Attempts were made to recover the smallest analyzable amounts and with maximal rapidity so that the sample would not consist of a mixture of portions of several passing boluses.

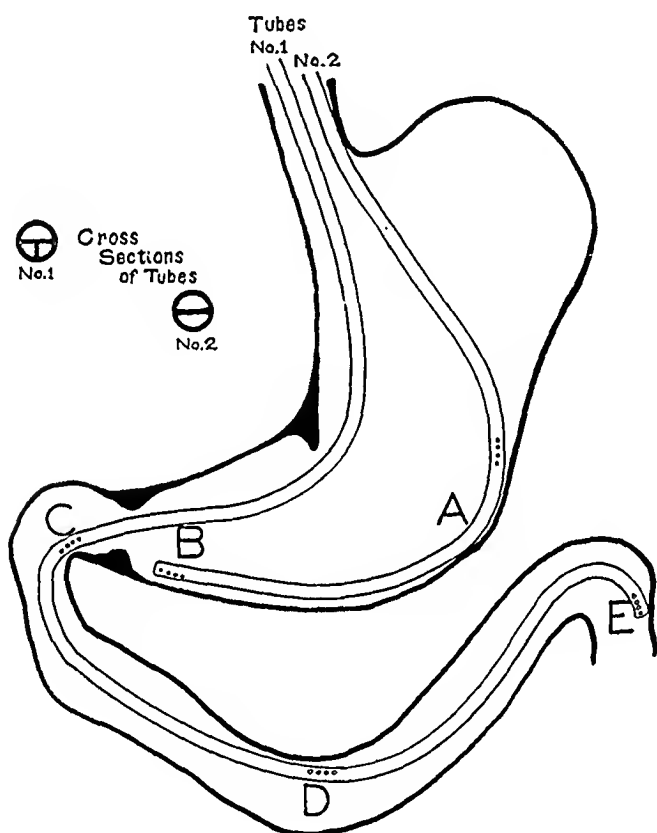


FIG. 1.—Arrangements of two- and three-lumen tubes in the stomach and duodenum. A, B, C, D and E indicate the sites from which samples were simultaneously removed at stated intervals after the ingestion of glucose solutions.

**Results.** Ten satisfactory experiments were performed. The data on 3 typical cases are shown in Chart 1. The fasting samples contained no glucose. Changing the concentration of the ingested solution made relatively little difference in the concentration of any of the subsequently removed duodenal specimens. From the ligament of Treitz area (E, Fig. 1) no specimen with a concentration over 6% was withdrawn, irrespective of the strength of the solution administered. So long as solutions of effective concentration were present in the stomach those recoverable from position E contained 2% to 6% of sugar. At the mid-duodenum the contents had a higher concentration, but characteristically they showed consider-

able variability. In some instances a rise from 4% to 13.4% occurred within 5 minutes in consecutive samples. A greater fall in the concentration occurred between the duodenal cap (C) and the mid-duodenum (D). This was to be expected, since the most irritable part of the intestinal tract lies between these two points. Reviewing the samples from all parts of the duodenum for the highest concentration recovered, however, it is interesting to note that, irrespective of the concentration of the specimens ingested, none containing more than 15% of glucose was ever recovered (Table 3), and that whenever a highly concentrated specimen was obtained, its volume was small.

TABLE 3.—HIGHEST CONCENTRATIONS FOUND IN DUODENUM AFTER INTRODUCTION OF HYPERTONIC GLUCOSE SOLUTIONS INTO STOMACH.

Exp. No.	Introduced.		Time of sampling (min.).	Concentration withdrawn.			
	%.	Vol. (cc.).		Pylorus (B) (%)	Duodenal cap (C) (%)	Mid- duodenum (D) (%)	Treitz ligament (E) (%)
142 . . .	25	200	36	18.0	7.5	12.4	
174 . . .	15	333	21	13.5	4.3	4.2	3.5
174 . . .	15	333	26	12.9	4.8	13.4	2.9
173 . . .	25	200	15	20.4	12.6	..	6.0
173 . . .	25	200	30	18.8	14.9	6.6	4.2
172 . . .	50	100	50	26.4	10.4	0.5	4.5

From the stomach specimens of far higher concentration were recovered, but these, for reasons to be discussed, are not strictly comparable to those from the duodenum. The rate of fall with time in the concentration of the total mixed gastric contents is given for 1 subject in Chart 2. The duration of the interval in which the concentration of the gastric contents exceeded the highest concentration for the duodenal contents in this instance was 52 minutes. The determination of this point may prove of real importance as indicating the duration of what are probably optimal conditions for duodenal absorption.

*Discussion.* The most important point determined by these experiments has been the maximal concentration of glucose that can leave the stomach. This figure is better obtained by observing the maximal concentration appearing in the duodenum, rather than the lowest concentration collectable from the stomach, as must become apparent on considering the differences in shape and activity of these two organs. The duodenum receives a bolus of gastric content and holds it for a brief period isolated from the material remaining in the stomach. During this interval the lively activity of its walls, the movement of the villæ, and the high ratio of mucosal surface to contained solution all facilitate the rapid dilution and absorption of the glucose contained.

In the stomach, on the other hand, the conical shape and active peristalsis of the antrum, in free communication as it must be with the capacious and inactive fundus, results in a very different rela-

tionship between the viscus and its contents. The deep peristalsis of the antrum results in so much better mixing of its contents than occurs in the fundus that the concentration of specimens from just proximal to the pylorus may be higher than those obtainable from the periphery of the fundus. At the same time, however, there may be a wide difference between the concentrations of fundus specimens taken from the central portion of the fluid contents and from the layer adjacent to the mucosa. If one considers a rapid transfer of fluid and possibly dissolved substances to occur through the gastric

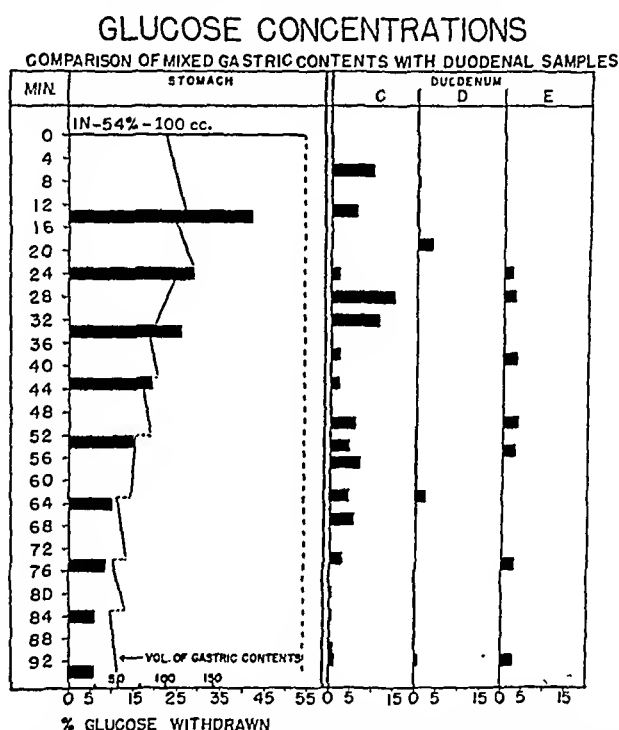


CHART 2.—The effect of a changing intragastric volume and concentration of glucose solution upon the concentration of the duodenal contents. At each time interval the stomach contents was completely removed, measured and all but a sample for analysis reinjected.

lining, the layer next the epithelium itself would be the one of lowest concentration. A peristaltic wave advancing along the conical antrum toward the pylorus will propel glucose solution toward a region of progressively diminishing diameter. The ratio of mucosal area to chyme volume momentarily increases. The fluid in the center of the antrum is forced orad, since it cannot advance, while, when the pylorus finally opens, it is the dilute peripheral layer of gastric contents which enters the duodenal cap. Since it has been impossible so far to recover this layer from the gastric side save in operated animals we feel that in the human the

duodenal eap contents represent the true character of the gastric content as it is expelled from the stomach. The fact that the stomach does not put out glucose in amounts proportional to the concentration administered has long been known, but the rôle of the shape of the viscera in modifying the flow of contents as distinct from any selective reflexes has not been emphasized.

**General Discussion.** The results given above are of interest chiefly for two reasons: 1, They probably represent the changes taking place in the upper digestive tract of normal man after the eating of sweets, and 2, they indicate the remarkable extent to which the major portion of the small gut is protected from wide variations in the character of its contents. These observations on man are of interest in relation to observations carried out by other workers on animals. Auchincloss, Macleod and Magee<sup>2</sup> have observed that in excised intestine  $\frac{3}{4}$  molar (13.5%) was the concentration of glucose that most rapidly traversed the gut wall. Magee and Reid,<sup>8</sup> carrying on this study *in vivo*, found indications that this concentration likewise is that at which glucose solutions most rapidly leave the stomach and enter the blood stream. Table 4 indicates the highest intestinal glucose concentration obtained by

TABLE 4.—PREVIOUSLY REPORTED FIGURES ON GLUCOSE CONCENTRATIONS.

Authors.	Animals.	Glucose.		Time (hrs.).
		Concentration into stomach (%).	Highest concentration out of intestine (%).	
Ravdin, Johnston and Morrison <sup>10</sup>	Dog	50	5.3	1
Cori <sup>3</sup>	Rat	80	14.2	3
Donhoffer <sup>4</sup>	Rat	76-18	12-8	1
Magee and Reid <sup>8</sup>	Rat	54	7.5	1-2
Macleod, Magee and Purves <sup>7</sup>	Rat	54	11.4	2

workers on intact animals after the introduction of solutions into the stomach. While Ravdin, Johnston and Morrison<sup>10</sup> recovered relatively low concentrations, the significant fact is that the highest concentration recovered by anyone was 14.2%. With these findings our observations upon the normal human stomach and intestine are in complete agreement and it would therefore appear that a concentration of 12% to 15% or about  $\frac{3}{4}$  molar, which incidentally is about the maximal concentration of glucose naturally occurring outside a cell, must be exceeded before gastric emptying is delayed and the stomach forced to play a part in the reduction of the concentration of its contents.

**Conclusions.** 1. There is no appreciable delay in the entry of glucose into the duodenum after the ingestion of a concentrated solution.

2. Following the ingestion of glucose solutions a far greater proportion of the sugar is absorbed from the gastro-duodenal region than from the jejuno-ileal region.

3. The range of glucose concentration from the cardia to the upper jejunum is from the concentration ingested to approximately 4% to 6%.

4. The maximal concentration at which glucose solutions usually enter the duodenum is 15% or less.

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### INTUBATION STUDIES OF THE HUMAN SMALL INTESTINE.

#### XIV. THE ABSORPTION OF GLUCOSE FROM THE DUODENUM.\*

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PREVIOUS investigation in this clinic<sup>2</sup> has shown that when a glucose solution is administered by mouth to a normal human subject only a small part of it reaches the duodeno-jejunal junction. The remainder presumably is absorbed in the stomach, the duodenum or both. In an attempt further to localize the place of disappearance the absorptive capacity of the duodenum alone for glucose has been studied with the results hereinafter recorded.

**Method.** Previous experience in quantitative studies of intestinal absorption in man had convinced us that the duodenum is the most difficult region of the entire digestive tract to isolate by mechanical means because of its great activity, its wide range of internal pressures and the ease with which its motor function is disturbed by extrinsic factors. It was necessary, therefore, to take unusual precautions for accuracy, including a very complicated apparatus and the selection of especially well-trained professional subjects.

\* Aided by grants from the Committee on Scientific Research of the American Medical Association, and from Smith, Kline and French Laboratories.

**Subjects.** Four normal women who had served as paid subjects for many other complicated experiments were selected. They were emotionally stable and had had a careful history, physical examination, gastric analysis and barium meal to establish their normal status. Their ages, weights, heights and surface areas are recorded in Table 1. No food or fluid was allowed for at least 9 hours before the experiment.

**Apparatus.** An arrangement of tubes was used which enabled us to maintain a constant flow of solution of known concentration into the duodenum and to recover all that was not absorbed. A device composed of 4 tubes was usually employed (Fig. 1). Tube D was of  $\frac{1}{32}$  inch outside

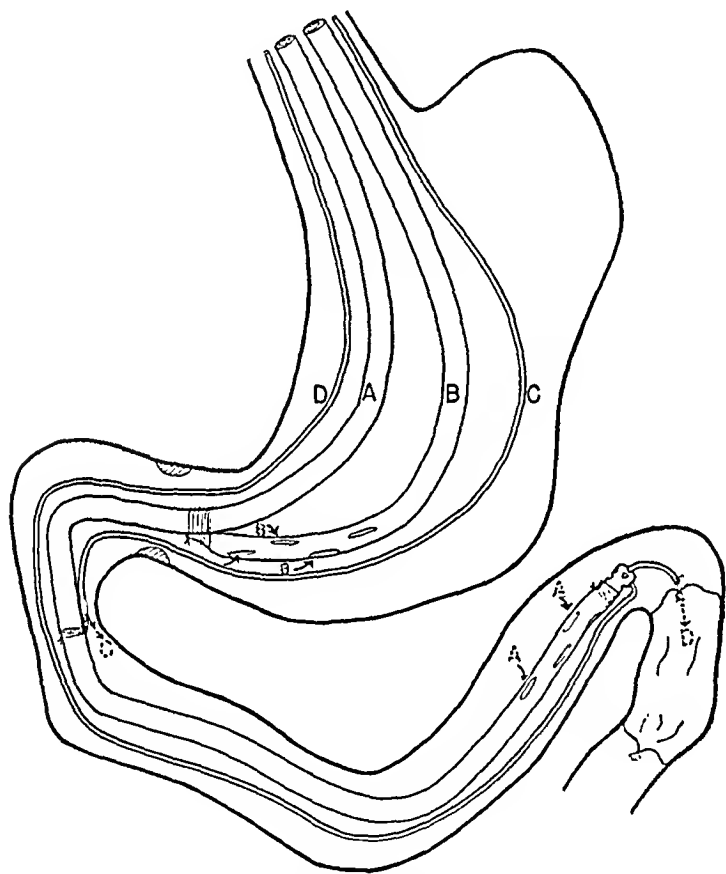


FIG. 1.—Diagram of the apparatus used in studying the rate of duodenal absorption. (See "Procedure" in text.)

diameter and  $\frac{1}{64}$  inch inside diameter and led to a thin rubber balloon D capable of holding 50 to 100 cc. of air. Tube A was of 5.3 mm. outside diameter and ended at the balloon D. For its last 3 cm. it was perforated with many holes A. Tube C, the same size as D, was fastened to Tube A. Its opening C lay 15 cm. proximal to the balloon D. Tube B, the same size as Tube A, ended 5 cm. proximal to C and was perforated with many holes for the last 15 cm. of its length.

**Procedure.** The technique employed was ordinarily as follows, minor variations being adopted when they were indicated. With the balloon deflated, the tubes were swallowed and by fluoroscopic manipulation they



were so placed that the balloon *D* lay just distal to the duodeno-jejunal junction, the Tube A ended at the ligament of Treitz, the opening *C* lay in the descending duodenum and the Tube B ended at the pylorus but sagged into the most dependent portion of the stomach. The subject lay supine on a fluoroscopic table, the head of which was raised to approximately 60° from the horizontal. All fasting contents of the stomach and duodenum were aspirated and thereafter constant suction, maintained at -100 cm. of water, was applied to Tubes A and B. Balloon *D* was then inflated to occlude the jejunum. A 300 cc. test solution of 15% glucose in warm water was injected through Tube C at a rate of 10 cc. per minute. At 5-minute intervals a fluoroscopic tracing on celluloid was made of the exact position of the tubes. At the end of 30 minutes the stomach and duodenum were washed out with the utmost rapidity in the following order. Into Tube A 50 cc. of water were rapidly injected and withdrawn. At the same time 250 cc. of water were quickly swallowed and aspirated from the stomach by Tube B. Into Tube C 50 cc. of water were injected and recovered from Tubes A and B. All tubes were then withdrawn slowly, constant suction being maintained on Tubes A and B as they came out. If the withdrawal caused vomiting the vomitus was saved.

TABLE 1.—EXPERIMENTAL SUBJECTS—PERSONAL DATA.

Subject.	Age (years).	Height (inches).	Weight (lbs.).	Surface area (sq. M.).
Hn. . . . .	34	66½	216	2.08
Hl. . . . .	35	65	129	1.63
Pr. . . . .	43	66½	180	1.90
Ps. . . . .	46	64	124	1.58

The absorption by the duodenum was calculated as follows: From the glucose given, the total amount recovered by all routes was subtracted. The jejunal peristalsis during the half-hour absorption period sometimes drew the balloon several centimeters into the jejunum, pleating the gut on the tube and exposing the sugar solution to jejunal mucosa. From the tracings of the tube at each 5-minute fluoroscopy the ratio of the length of the duodenum to the length of the exposed portion of the jejunum was determined. The total absorption was apportioned to the duodenal and the jejunal units in proportion to the average ratio. It is realized that the rate of absorption is probably somewhat greater in the duodenum than in the upper jejunum and that where much of the jejunum was included in the absorption area an error is introduced by this method of calculation. However, the consistency of the results appear to justify its use.

So many sources of technical error were possible in this procedure that it was felt wiser to vary the details of the process frequently, lest some undetected constant error warp the findings. As none of them appears to have had a significant effect upon the results the typical procedure only has been given.

**Results.** From 20 experiments 13 were selected as being technically satisfactory. The results of these (Table 2) show an absorption capacity for the duodenum of from 6.3 to 19 gm. per hour.

**Discussion.** The point of this procedure was to keep the duodenal mucosa constantly bathed with a fresh solution of glucose throughout a stated period, so that an excess of sugar should always be present at as nearly a known concentration as possible. The wide variation in absorption figures is interesting from the standpoint of individual variations. The lowest figure, 6.3 gm. per hour,

occurred on an occasion when Ps. was given a 5% solution. From the same solution Pr. absorbed twice as much, while from a 10% solution Hn. absorbed 1.9 gm. per hour more than the highest absorption rate attained by Pr. from a 15% solution. Nevertheless, though Hn. took up 19 gm. per hour from a 10% solution on 1 day, she only absorbed 8.5 gm. per hour from a 15% solution at another time. While these variations would occur, were we failing to recover all the unabsorbed glucose injected, we have come in the course of time and by virtue of many carefully controlled experiments to feel that under the circumstances of these selected experiments no glucose solution was escaping past the balloons. We are prepared then to believe that people have their good days and their bad days and that the rate of glucose absorption is rather variable from time to time in the same individual.

TABLE 2.—DUODENAL ABSORPTION OF GLUCOSE.

Subject.	Glucose given.		Absorption time (minutes).	Total absorption (gm./hr.).	D/J* length ratio (%).	Duodenal absorption (gm./hr.).
	%.	Gm.				
Pr. . . .	5	15	23	17.8	71	12.6
Hn. . . .	5	15	30	11.8	83	9.8
Ps. . . .	5	15	32	8.8	72	6.3
Ps. . . .	5	15	32	12.5	61	7.6
Hn. . . .	10	30	30	25.0	65	15.8
Pr. . . .	10	25	29	32.8	29	9.2
Hn. . . .	10	24	27	19.0	100	19.0
Hl. . . .	15	15	30	11.7	100	11.7
Pr. . . .	15	45	27.5	15.2	50	7.6
Hn. . . .	15	45	30	21.6	60	12.9
Pr. . . .	15	19.5	24	20.0	57	11.4
Hn. . . .	15	15	21	21.1	40	8.5
Pr. . . .	15	37.5	27.5	28.8	56	17.1

\* Duodenal/jejunal.

This series of experiments would appear to be sufficient to warrant the conclusion that if the duodenum receives its normal concentration of glucose—shown by previous studies to be not over 15%—then 20 gm. per hour would usually represent the maximal absorption capacity of the duodenum.

Although the experiments here recorded are not strictly comparable to those by which we studied the absorption rate of the lower small gut,<sup>1</sup> it appears that the duodenum absorbs glucose appreciably more rapidly than do the jejunum and the ileum. While we have no evidence on the relative power of the individual epithelial cells to perform this function at the different intestinal levels, the studies of Warren<sup>3</sup> on the relation of the intestinal length to the mucosal surface area suggest that the observed differences in the absorption rate may be due simply to the greater number of epithelial cells per unit length of gut at the proximal as compared to the distal end of the intestine.

The implications of these experiments with regard to the areas proximal to the duodeno-jejunal junction from which glucose is absorbed is their chief importance. It becomes immediately apparent in reviewing experiments in which glucose given by mouth is recovered from the beginning of the jejunum that more glucose has been absorbed proximal to that point than could be removed by a duodenum absorbing 19 gm. per hour.<sup>2</sup> While this is only true in those instances in which solutions of high concentration are given, it forces a consideration of the question of gastric absorption. Attempts to obtain direct evidence on this point are recounted in another paper.

**Summary.** 1. The duodenum absorbs glucose very rapidly as compared to other regions of the alimentary canal of equal length and at a rate that varies in the individual from day to day.

2. Though as little as 6 gm. per hour has been absorbed from dilute solutions, the maximal rate from solutions within the normally occurring concentration range is about 20 gm. per hour.

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### CLINICALLY ASSOCIATED DEFICIENCY DISEASES.\*

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THE period during which brilliant investigations led to the isolation, synthesis and clinical evaluation of thiamin, nicotinic acid, riboflavin, and vitamin B<sub>6</sub> has been followed by one of confusion. The literature in regard to these vitamins and the deficiency diseases arising from a lack of them is vast and often contradictory. Continued research concerning the members of the vitamin B complex and their relation to deficiency states and to each other is necessary for the problem is complex and precise knowledge is meager (Fig. 1). Nevertheless, our studies of clinically associated deficiencies indi-

\* The heavy burden of expenses necessary for this work has in large part been borne by the John and Mary R. Markle Foundation, Anhaeuser-Busch, Inc., and Eli Lilly and Company.

cate that the application of certain principles and methods of therapy is followed by spectacular improvement in the health and well-being of these persons.

The present report is concerned with studies conducted in Jefferson County, Alabama, and Hamilton County, Ohio. In a series of 1250 consecutive malnourished persons, we have studied the predisposing causes, development, early diagnosis and specific therapy of nutritional diseases. The studies reported in this communication were begun February 1, 1938, and extended through April 30, 1940. They are being continued, but the results to date are such as to warrant the following report.

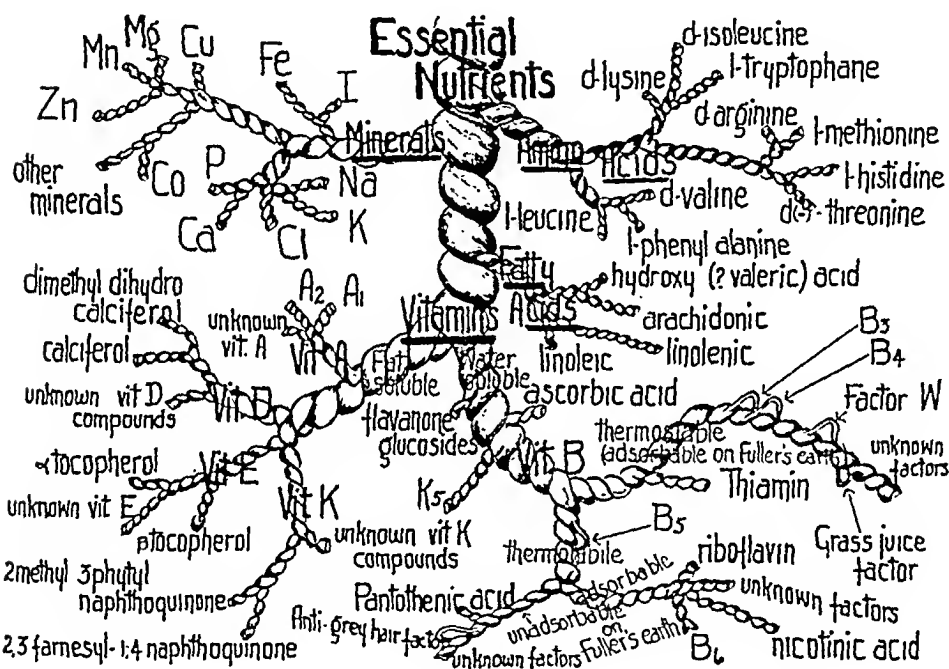


FIG. 1.—Differentiation of some of the essential nutrients. It seems especially pertinent to separate the fat-soluble and water-soluble vitamins. Some are known only by physiologic properties and few as yet have been shown to be specific for human diseases.

**Method.** The subjects were selected from persons presenting themselves for examination either at the Hillman Hospital, Birmingham, Ala., or the General Hospital, Cincinnati, Ohio. The patients made frequent visits to the clinic, and at the time of each visit they were weighed, examined, and medical and dietary histories were taken. Home surveys of 50 cases were made to ascertain what the patients actually ate. As soon as a diagnosis of nutritional deficiency was made, responsibility was immediately assumed and study begun. The diagnosis of a specific deficiency state was based on the presence of symptoms characteristic of it. For example, a diagnosis of pellagra was made only if characteristic mucous membrane lesions, dermal lesions, or both, were present; a diagnosis of riboflavin deficiency depended upon the presence of characteristic angular lesions of the mouth,

or ocular symptoms; a diagnosis of beriberi was made only in the presence of nutritional neuritis. The diagnosis in each instance was confirmed by the response of the patient to the specific therapeutic agent, administered under controlled conditions. In general, the method of confirmation consisted in the dramatic response of the patient to the administration of synthetic nicotinic acid or its compounds, synthetic riboflavin, or synthetic thiamin hydrochloride, or synthetic vitamin B<sub>6</sub>, the patient's diet remaining constant. Many of these patients had other diseases, such as scurvy, which was treated with synthetic cevitamic acid, and vitamin A deficiency, which responded to carotene or oleum percomorphum. Some of the patients after being treated with specific therapeutic agents were given either liver extract or dried brewer's yeast as supplements to their diets.

AVERAGE DIET OF FIFTY PELLAGRINS COMPARED WITH ADEQUATE DIET.

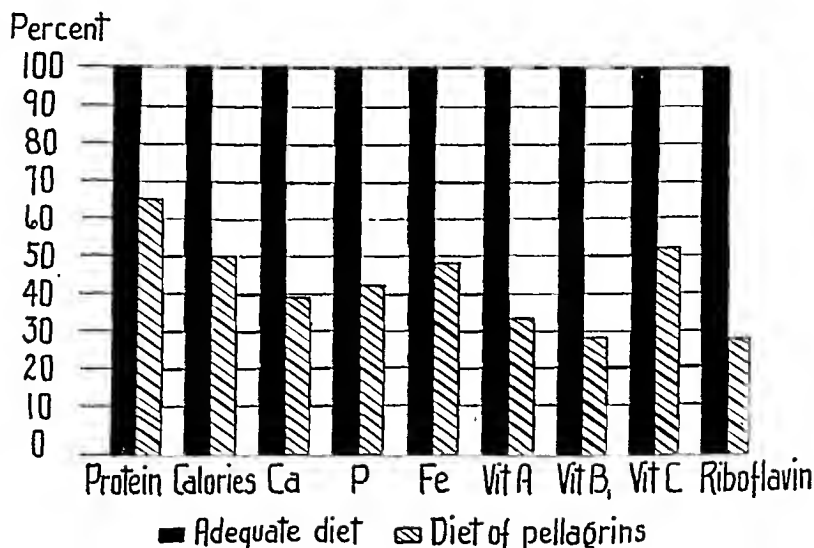


FIG. 2.—These dietaries are typical of those used by other members of the family and by neighbors who did not have clinical pellagra during the course of the study.

**Observations. Dietary.** That general malnutrition must be present in many of these persons even though they have no symptoms of a specific deficiency disease is indicated by a detailed analysis of the dietaries of 50 cases which shows that they are deficient to some extent in each of the essential nutrients. An accurate record of all the food eaten by each patient was kept for a period of 1 week. During this time, frequent visits to the home were made to determine the size of the portions of food used and the method of preparing it. Using the most accurate available information on the composition of foods, the total content of calories, vitamins, protein, and minerals in the food consumed by each patient in 1 week was calculated, and from this the average daily intake was determined. The nicotinic acid and vitamin B<sub>6</sub> content of foods is too little known to warrant evaluating the dietaries in respect to these vitamins.

Human nutritional requirements cannot be stated with absolute precision, but Stiebeling has estimated the quantities of nutrients required daily by the average individual; we may thus assess approximately the deficiencies in the dietaries of these persons (Fig. 2).

1. *Calories.* The average person received only 50% of his estimated energy requirement.

2. *Protein.* The protein intake of the average individual in this group was 35% below the desirable amount. The average intake of 0.68 gm. per kilo of body weight was above the maintenance requirement of 0.5 gm. per kilo calculated by Sherman, but did not approach the 1 gm. per kilo which is recommended as a liberal daily allowance; this optimum level was reached by only 5% of the patients. On the other hand, 35% of them received less than 0.5 gm. per kilo and were undoubtedly suffering from the effects of this low nitrogen intake.

Mitchell has shown that lysine and tryptophane are limiting factors in the growth of young animals receiving their protein entirely from whole corn, and that lysine is a limiting factor in the case of wheat flour. In the majority of these 50 dietaries, a large part of the total protein was furnished by grain products, and if the remainder of the protein were also low in lysine and tryptophane content, a specific deficiency of these two amino acids might be expected. In three-fourths of the cases studied, however, more than 10% of the total protein came from animal sources and was of excellent biologic quality. Sherman has shown that such a mixture of grain and animal proteins is adequate for nitrogen equilibrium in adults even at low levels of intake. The remaining fourth of the patients ate enough vegetables to supply an average of 35% of their total protein intake. The proteins of many vegetables are inferior in biologic value when fed as the sole source of nitrogen; Mitchell has shown that this is due to a low content of the sulphur-containing amino acids in the case of navy beans, garden peas, and potatoes. It is likely, however, that vegetable proteins supplement those of grain products to some extent.

The total protein intake in at least 35% of the cases studied is too low to maintain nitrogen equilibrium. Whether this results in a specific or a general amino-acid deficiency is uncertain.

3. *Minerals.* Nearly all the patients received sub-standard amounts of calcium, phosphorus and iron, and none of them obtained standard amounts of all three elements. In two-thirds of the 50 cases, the intake of these minerals was not sufficient to meet even the maintenance requirement. About 72% of the patients were probably losing calcium and phosphorus. Although iron deficiency was less marked than that of calcium and phosphorus, 64% received less than 8 mg. of iron daily with an average intake of 4.8 mg.; 10% obtained less than 4 mg. daily. Undoubtedly such

restricted iron intake, if continued long enough, will predispose to anemia.

4. *Vitamins.* Suboptimal amounts of all the vitamins were furnished by the dietaries examined. The average diet fell below the suggested standards for normal persons approximately as follows: vitamin A, 67%; vitamin B<sub>1</sub>, 72%; vitamin C, 47%; and riboflavin, 73%. From these results, it appears that the deficiency of vitamin C is not as marked as that of the other vitamins. It must be remembered, however, that these figures represent the average intake of the group. Several individuals consumed diets in which there were no foods containing vitamin C.

An examination of these dietaries leaves little doubt that patients subsisting on them are malnourished and prone to develop mixed deficiencies.

*Clinical.* There was great improvement in every person treated. Approximately 30% were able to obtain positions and work steadily, whereas they had previously had years of ill-health which interfered with their ability to work. Following the administration of nicotinic acid or nicotinic acid amide, or other potent substances related to this compound, there was prompt disappearance of the mucous membrane lesions of pellagra, healing of the dermal lesions, and disappearance of the mental symptoms due to pellagra. There was also an increase to normal or above in the concentration of Co-enzymes I and II in the blood, and disappearance of abnormal pigments in the urine. Following the administration of vitamin B<sub>1</sub>, there was improvement in the patient's general condition and prompt amelioration of the symptoms arising from neuropathy or edema. The administration of riboflavin caused the disappearance of the dermal lesions and ocular symptoms characteristic of riboflavin deficiency within a week. The administration of synthetic vitamin B<sub>6</sub> was followed by prompt disappearance of the extreme nervousness, insomnia, irritability and abdominal pain, and the patients were able to walk without difficulty. A number of the patients were treated successfully for anemia, scurvy, and vitamin A deficiency. As a rule, there was prompt improvement in the syndrome for which the chemical substance is specific following its administration, whereas the symptoms of associated syndromes did not improve so long as the diet remained constant.

Although the administration of a single chemical substance was followed by a remarkable response of the lesion for which it was specific and by a great increase in the patients' strength, the improvement of the patients in general was greater when they were given a number of synthetic materials than when they were given any one alone. Furthermore, when supplements of dried brewers' yeast powder (Anhaeuser-Busch, Inc., Mead Johnson and Company, and the Harris Laboratories, Inc.) or liver extract (Eli Lilly and Co.) were given in addition to synthetic materials to persons who con-

tinued to eat their usual inadequate diets, there was an even greater improvement in their general health.

**Summary and Conclusions.** Twelve hundred and fifty persons with clinically associated deficiency disease syndromes have been treated without a fatality, whereas the mortality rate a few years ago was 54%. The clinical studies of these persons and analysis of their diets indicate that they have a deficiency in calories, protein, calcium, phosphorus, iron, and the known vitamins. They have mixed rather than single deficiency diseases, and months and years of ill-health precede any diagnostic lesions of a specific deficiency. Part of the confusion in the literature regarding vitamins and deficiency diseases is due to the discovery that vitamin B, which was formerly considered a single substance, is composed of 12 or more separate factors, each, together with unknown substances, contributing to the total effect of therapeutic agents such as yeast, wheat germ, or liver extract. These studies suggest that from the standpoint of practical application, mixed vitamin therapy is often desirable. In our hands, the administration of water-soluble vitamins, together rather than individually, and the fat-soluble vitamins, together rather than individually, has a definite usefulness in our day to day treatment of these deficiency states.

Invaluable aid was given by the administrative and professional staffs of the General Hospital and the Hillman Hospital, and we are particularly indebted to Drs. R. W. Vitler, W. B. Bean, C. D. Aring, H. S. Sehiro, J. B. McLester, S. L. Applebaum, D. P. Hightower, L. H. Hubbard, T. S. Booser, A. W. Woods, J. P. Frostig, H. E. Himwich, and F. H. Lewy. Technical assistance was given by Mrs. S. P. Vilter and Mrs. M. B. Koch; and nursing service, by Mrs. A. W. Mann, Miss Monette Springer, and Miss Verna Moore.

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## VITAMIN C IN EPILEPSY.

### DILANTIN SODIUM NOT A CAUSE OF VITAMIN C DEFICIENCY.\*

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ONE of the side effects in patients with epilepsy who are being treated with dilantin sodium is swelling of the gums. This swelling is a benign hyperplasia and in most instances is not noticed by the patient. Kimball<sup>5</sup> reported this gingival hyperplasia in 57% of his patients and expressed the belief that it was due to a deficiency

\* The study was aided by a grant from the Parke, Davis & Company.



in vitamin C induced by the drug. He did not offer adequate evidence for this hypothesis since none of the other symptoms of scurvy were present and the average vitamin C content of the plasma of patients who had gingival hyperplasia was not lower than would be expected in his patients, who were pupils in the Detroit free school for epileptics and were from the lower economic levels of society. In addition, his administration of large amounts of vitamin C produced no change in the abnormal condition of the gums even though the plasma vitamin C content was raised thereby to well above the normal level. Gruhzt,<sup>3</sup> working with animals, found that the administration of dilantin sodium had no effect on the absorption or utilization of vitamin C. The occurrence of prominent swelling of the gums in about 3% of our patients under treatment with dilantin sodium led us to make a study of the vitamin C content of the plasma of as many of our patients with convulsive seizures as possible, regardless of the type of therapy being administered.

**Method and Results.** Venous blood was withdrawn from the patients and the vitamin C content of the plasma determined by the method of Farmer and Abt.<sup>2</sup> The protein-free filtrate was made within 15 minutes of withdrawal of blood, and the titrations performed within 2 hours.

Determinations were made on the plasma of 257 patients. The majority of these determinations were on ambulatory patients attending the outpatient department of the Boston City Hospital. The remainder were on private patients. None were taking a special diet. The results obtained are grouped with reference to the type of therapy which the patients had been receiving and are shown in Table 1.

TABLE 1.—THE VITAMIN C CONTENT OF THE PLASMA OF PATIENTS WITH "EPILEPSY."

Type of medication.	No. of patients.	No. of determinations.	Vitamin C content of plasma (in mg. per 100 cc.).		
			High.	Low.	Average.
None . . . . .	31	32	1.2	0.05	0.46
Phenobarbital . . . . .	44	47	1.6	0.00	0.45
Dilantin sodium . . . . .	182	207	1.6	0.05	0.44

The range of the plasma levels of vitamin C and the average value for the three groups of patients receiving: 1, no treatment; 2, phenobarbital; and, 3, dilantin sodium, respectively, were almost identical.

To determine whether the long continued administration of dilantin sodium had any effect on the vitamin C level of the plasma, the results in 182 patients receiving this medication were divided into groups with reference to the length of time each group had been receiving it. The results as shown in Chart 1 indicate that there was no appreciable difference in the vitamin C content of the plasma of patients who had been taking dilantin sodium for 2 years from that of the patient who had never received this medication. To

further check this observation, the determination was repeated in 25 patients after 5 months of treatment. The results were identical in 8, there was a slight or moderate increase of vitamin C in 10, and a slight or moderate decrease in 7 patients.

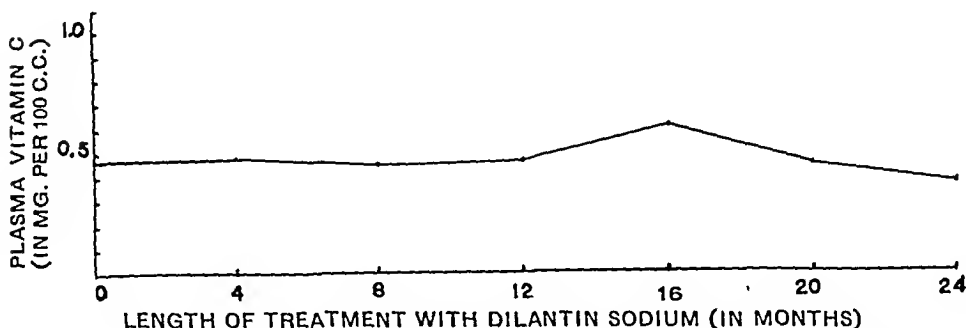


CHART 1.—The relationship of the vitamin C content of the plasma to the length of treatment with dilantin sodium.

Forty of the 182 patients (22%) who were receiving dilantin sodium therapy had some degree of gingival hyperplasia which was not present before treatment began. In only 5 patients (3%) was the swelling severe enough to cause discomfort. The vitamin C content of the plasma bore no relationship to the presence or absence of this symptom (Table 2). The average content in the 40 patients with swollen gums (0.44 mg. per 100 cc.) was exactly the same as that of the 142 patients without this symptom.

TABLE 2.—THE RELATIONSHIP OF THE VITAMIN C CONTENT OF THE PLASMA TO THE DEGREE OF GINGIVAL HYPERPLASIA IN PATIENTS UNDER TREATMENT WITH DILANTIN SODIUM.

Severity of gum swelling.	No. of patients.	Vitamin C content of plasma (in mg. per 100 cc.).		
		High.	Low.	Average.
None . . . . .	142	1.66	0.05	0.44
Mild . . . . .	20	1.10	0.10	0.40
Moderate . . . . .	15	1.30	0.10	0.50
Severe . . . . .	5	0.76	0.12	0.40

TABLE 3.—THE EFFECT OF THE ADMINISTRATION OF FOODS HIGH IN VITAMIN C CONTENT ON THE PLASMA VITAMIN C LEVEL IN 16 PATIENTS UNDER TREATMENT WITH DILANTIN SODIUM.

	Vitamin C content of plasma (in mg. per 100 cc.).		
	High.	Low.	Average.
Before . . . . .	0.62	0.07	0.22
After . . . . .	1.77	0.43	1.12

To test the effect of administration of vitamin C by mouth on the plasma vitamin C content of patients under dilantin sodium therapy, 16 patients with a low level were requested to eat 4 oranges and drink a glass of tomato juice daily for periods ranging from 1 to 2 months while continuing the use of dilantin sodium. There was a prompt rise in the plasma content of all of these patients from an

average level of 0.22 to 1.12 mg. per 100 cc. (Table 3). The swelling of the gums which was present in 12 of these 16 patients was not affected by this diet.

**Discussion.** The vitamin C content of the plasma of apparently healthy individuals on a well balanced diet is usually between 0.8 and 1.2 mg. per 100 cc. The results of determinations in large numbers of individuals with no signs or symptoms of scurvy show a variation over a much wider range,<sup>7</sup> and it may be stated that the vitamin C content of the plasma of an individual represents the relative dietary intake of vitamin C in the preceding few weeks. Because foods rich in vitamin C are relatively expensive, it is not surprising that the plasma vitamin C content of patients in the low economic groups or in institutions for the care of the mentally or chronically ill<sup>1,8,9</sup> is much lower than that usually reported as normal. In our group of patients the average value (0.45 mg. per 100 cc.) was only half of the lower limit of normal but this value is similar to that reported by Lund<sup>6</sup> for patients admitted to the surgical service of this hospital and in agreement with the reports from hospitals for chronically ill patients. The average value for the 23 private patients in our group who were taking dilantin sodium was 0.8 mg. per 100 cc. This is further evidence that the level of vitamin C in the plasma is influenced by economic factors. Herlitz<sup>4</sup> studied hyperplastic gingivitis in dental patients with no symptoms of scurvy and found no relationship between the gingivitis and the vitamin C content of the plasma.

**Summary.** 1. The plasma vitamin C content of 257 ambulatory patients with convulsive seizures varied between 0.0 mg. and 1.6 mg. with an average of 0.45 mg. per 100 cc.

2. The plasma vitamin C content of these patients was in no way influenced by the type of therapy they were receiving.

3. The long continued administration of dilantin sodium had no effect on the vitamin C level of the plasma and did not influence the absorption of vitamin C when given by mouth.

4. Hypertrophic gingivitis developing in patients under treatment with dilantin sodium is not related to the vitamin C content of the plasma or to the utilization of vitamin C.

5. The low level of vitamin C in the plasma of clinic patients with epilepsy is due to an inadequate intake of this element, because the administration of food with a vitamin C content to a group with low values resulted in a 5-fold increase.

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## BOOK REVIEWS AND NOTICES

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**THE EMPEROR'S ITCH.** The Legend Concerning Napoleon's Affliction With Scabies By REUBEN FRIEDMAN, M.D., Assistant Professor of Dermatology and Syphilology, Temple University School of Medicine, Philadelphia. Pp. 89; 10 illustrations. New York: Froben Press, 1940. Price, \$1.50.

THE author discusses the legend of Napoleon having been affected with scabies. He suggests that Napoleon may have had dermatitis herpetiformis, and it is not surprising that his evidence for this is unconvincing, since the diagnosis of this disease often presents difficulty in living patients. Portions of the book are interesting, but its publication as a monograph hardly seems justified.

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**DERMATOLOGIC THERAPY IN GENERAL PRACTICE.** By MARION B. SULZBERGER, M.D., Assistant Clinical Professor of Dermatology and Syphilology, Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital of Columbia University; Associate Attending Dermatologist, Montefiore Hospital, New York City, and JACK WOLF, M.D., Attending Dermatologist and Syphilologist, Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital of Columbia University; Director of Dermatology, New York City Cancer Institute. Pp. 680; 65 illustrations and 25 tables. Chicago: The Year Book Publishers, Inc., 1940. Price, \$4.50.

IN this volume the authors have set down in concise, clear, and detailed fashion the methods of dermatologic therapy which seem best and most effective for use by the physician not especially trained in dermatology. They discuss only those diseases which are relatively common and "make up perhaps 90 per cent of all dermatologic cases." They have properly omitted the details of special and complex methods of treatment which may best be carried out by the dermatologist or the dermatologically-minded roentgenologist, surgeon, or allergist.

The senior author, in particular, has for the past decade been establishing himself as a competent experimenter in dermatology and as one of the most literate and intelligent interpreters of changes of the skin in the light of immunologic and other basic physiologic studies. It is immediately apparent that the authors do not regard the prescribing of lotions and ointments as the more important part of skin therapy. Proper emphasis is laid upon the methods of obtaining an intelligent and searching history and of examining the skin, upon the rationale of allergic study (with justifiable indication of the ineptness of much of the ordinarily employed scratch and intradermal test methods in urticaria and contact dermatitis), upon the value of a general medical approach to many dermatoses, and upon the easily available methods of laboratory diagnosis. The illustrated instructions for the application of local medication of varying types to different parts of the skin and the many practical details for increasing the acceptability of messy methods of treatment are extremely valuable. Reference is made to many useful proprietary medicines and foods, always with a helpful indication of where these preparations may be obtained.

As in other fields of medicine, a considerable portion of dermatologic treatment is on an empiric basis, and it is inevitable that the informed reader will disagree on some minor points. For example, the inclusion of

manganese injections and of tin salts orally in the list of treatments for acne can hardly be endorsed. The occasional essential importance of orthopedic measures in the treatment of plantar warts is not mentioned. The section on syphilis is brief and does not approach in completeness those on dermatologic therapy. The tone of personal authority is lacking in this chapter, and to this Reviewer its inclusion in a book on dermatologic therapy seems unnecessary and anachronistic.

The volume cannot fail to be extremely valuable to the specialist in dermatology as well as to the general practitioner. While its broad classification of dermatoses is simple, the extremely helpful differential diagnostic lists and discussions include many terms which imply a reasonably good working knowledge of dermatology on the part of the reader. However, as the authors state, this book is not offered as a complete text, but as a supplementary practical source of information which, to this Reviewer's knowledge, is not available in any other single volume. It is a credit to the authors and to the field of dermatology. D. P.

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OBSERVATIONS MADE DURING THE EPIDEMIC OF MEASLES ON THE FAROE ISLANDS IN THE YEAR 1846. By PETER LUDWIG PANUM, M.D. (Translated from the Danish by ADA SOMMERVILLE HATCHER). With a Biographical Memoir by JULIUS JACOB PETERSEN, M.D. (Translated from the Danish by JOSEPH DIMONT), and an Introduction by JAMES ANGUS DOULL, M.D. Pp. 111. Published by the Delta Omega Society. Distributed by the American Public Health Association, New York City, 1940. Price, \$2.50.

THE Delta Omega Society has from time to time sponsored the republication of public health classics that are not generally available to students of public health. The present volume is Panum's report upon the epidemic of measles in the Faroe Islands, one of the most famous and complete of all epidemiologic studies. Brought to the highly susceptible population of the Faroes by an islander on his return from Copenhagen, measles attacked 97% of the inhabitants, resulting in some 5000 cases and 102 deaths. The first medical writing of its young author, the report remains a masterpiece that makes fascinating reading nearly a century after its appearance. The Delta Omega Society is to be congratulated upon its selection. R. K.

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GYNECOLOGICAL AND OBSTETRICAL PATHOLOGY. With Clinical and Endocrine Relations. By EMIL NOVAK, A.B., M.D., D.Sc. (Hon. Dublin), F.A.C.S., Associate in Gynecology, The Johns Hopkins Medical School; Gynecologist, Bon Secours and St. Agnes Hospitals, Baltimore, etc. Pp. 496; 427 illustrations. Philadelphia: W. B. Saunders Company, 1940.

For some years there has been a need for a well balanced presentation of gynecologic and obstetric pathology. This need has been stimulated, no doubt, by the increasing interest in endocrinology and the relation of pelvic pathology to abnormalities of the menstrual cycle. Again, the requirements in pathology by the specialty examination board has stimulated the need for a book of this type. That Dr. Novak should be the author was logical from his long interest and experience in the subject. The text is exceptionally well balanced, particularly in the correlation of the pathologic physiology of the pelvic organs and clinical symptoms. The endocrinologic aspects of the subject has been very comprehensively presented, and includes a basic chapter on normal pelvic physiology.

In a logical order the various regions—vulva, vagina, cervix and so on, are taken up *in seriatim*. The discussion of kraurosis and leukoplakia clearly differentiates these much confused lesions. The author explains

the differences in the numerous methods of grading which have been offered. He emphasizes repeatedly the importance of serial sections and minimizes the advantages of colposcopy and the Schiller tinctorial test. Three chapters are devoted to the histology of the endometrium, a summary of cyclical and pregnancy changes in endometrium and clinical symptoms of hyperplasia of the endometrium. In discussing the difficulties which often arise in diagnostic curettage, the author quotes Halban, who after examining a doubtful specimen pronounced, "not cancer but better out." The writer states that sarcoma constitutes 4.5 per cent of uterine malignancy in his laboratory. This is a larger proportion than in most institutions and may probably be due to the fact, as he states, that a very large number of serial sections are made.

In the section devoted to the pathology of the ovary, the author devotes considerable space to the more recently described tumors such as dysgerminoma, granulosa-thecoma and arrhenoblastoma. This detailed discussion he feels has been necessitated through a lack of any full presentation of this subject elsewhere. The basic histogenesis of one group of these tumors leads him to suggest the inclusive designation "feminizing mesenchymoma of the ovary."

In the chapter on pelvic endometriosis following an extended discussion of its pathologic and clinical characteristics, the author gives an interesting summary of the various theories of the histogenesis of this condition. Following two complementary chapters on placentation and abnormal activity of the trophoblast, the book closes with a discussion, by Dr. L. M. Hellman, of other abnormalities and diseases of the placenta and appendages.

There are 427 illustrations in this book, the majority of them are carefully selected photomicrographs, appropriately correlating points brought up in the text. The text itself is remarkably free from quotations from the literature although a short, important bibliography is appended to each chapter. This book should fulfill a well defined need, should be of undoubted value to both physicians and pathologists, as well as serving as a textbook for those about to undertake examinations of the specialty board. P. W.

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**THE FOOT AND ANKLE.** Their Injuries, Diseases, Deformities and Disabilities. By PHILIP LEWIN, M.D., F.A.C.S., Associate Professor of Bone and Joint Surgery, Northwestern University Medical School; Professor of Orthopaedic Surgery, Post-Graduate Medical School of Cook County Hospital, etc. Pp. 620; 303 illustrations. Philadelphia: Lea & Febiger, 1940. Price, \$9.00.

An excellent treatise dealing with lesions of the foot and ankle. Written in a preëminently practical manner. Profusely illustrated with clear, pertinent halftone and line drawings.

Recommended not only to orthopedists but also to surgeons and general practitioners. G. W.

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**ATLAS OF CARDIOROENTGENOLOGY.** By HUGO ROESLER, M.D., F.A.C.P., Associate Professor of Roentgenology; Cardiologist in the Department of Medicine, Temple University School of Medicine and Hospital, Philadelphia. Pp. 124; 166 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, \$12.50.

Sixty cardiac case reports are presented with emphasis on the radiologic aspects. Collateral clinical and laboratory data, including electrocardiograms, are also given. Noteworthy is the correlation of the radiograms with the postmortem findings in 16 cases, the hearts being appropriately sectioned or windowed in each case. The unusually large illustrations are uniformly excellent. The examples of the different conditions causing

cardiovascular deformity are well assorted, but the variety of appearances in each of the diseased states is, in the Reviewer's opinion, insufficiently illustrated to make the atlas comprehensive. The method of presentation is commendable, and despite its incompleteness, the book is highly recommended to those specially interested in radiology and cardiology.

A. M.

**HEALTH IS WEALTH.** By PAUL DE KRUIF. Pp. 246. New York: Harcourt, Brace & Co., 1939. Price, \$2.00.

A RECORD of certain efforts in recent years to foster a national health program, together with an outline for such a plan. The author's part in these efforts is represented chiefly by a series of articles which were published in the "Country Gentleman," and which, here reprinted, constitute the bulk of the book. Written for laymen, it is frank propaganda for a cause which should also appeal to physicians. Unfortunately, as in so much propaganda literature, there is excessive use of the tremolo stop and some loose reasoning. Thus, in the proof offered for the statement that "more than half of our nation is less than half alive," are cited the two-odd million hay fever victims, as though their illness lasted all year. Nevertheless, physicians will find the book both interesting and timely.

R. K.

**RHEUMATIC FEVER.** Studies of the Epidemiology, Manifestations, Diagnosis and Treatment of the Disease During the First Three Decades. By MAY G. WILSON, M.D., The New York Hospital and Department of Pediatrics, Cornell University Medical College, New York City. Pp. 595; 78 illustrations and 5 appendices. New York: The Commonwealth Fund, 1940. Price, \$4.50.

ACCORDING to the introduction, "no attempt has been made to prepare a text book or a comprehensive critical review of rheumatic fever." Having thus disarmed her critics, the author proceeds to present the picture of rheumatic fever in a manner at once new, readable, and inclusive.

The results of statistical analysis are used to good effect, both in pointing out certain misconceptions and in establishing new relationships. Much material is condensed into tables or graphs. The chapters are brief. Frequent summarizing paragraphs and chapters assist the reader. Diagnostic procedures are fully described. The inclusion of tables for normal values makes the book a valuable source of reference.

W. J.

### NEW BOOKS.

*Atlas of Cardioroentgenology.* By HUGO ROESLER, M.D., F.A.C.P., Associate Professor of Roentgenology; Cardiologist in the Department of Medicine, Temple University School of Medicine and Hospital, Philadelphia. Pp. 124; 166 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, \$12.50. (Review p. 547.)

*Rheumatic Fever.* Studies of the Epidemiology, Manifestations, Diagnosis and Treatment of the Disease During the First Three Decades. By MAY G. WILSON, M.D., The New York Hospital and Department of Pediatrics, Cornell University Medical College, New York City. Pp. 595; 78 illustrations and 5 appendices. New York: The Commonwealth Fund, 1940. Price, \$4.50. (Review p. 548.)

*The Medical Clinics of North America (Volume 24, No. 4, Mayo Clinic Number, July, 1940).* Pp. 350; 37 illustrations. Philadelphia: W. B. Saunders Company, 1940.

In addition to a 9-article symposium on endocrine therapy, this number contains 14 papers which, as usual, cover a wide variety of subjects.

*The Universe Through Medicine.* By J. E. R. McDONAGH, F.R.C.S. Pp. 389. London: William Heinemann (Medical Books) Ltd., 1940. Price, 25s.

*Your Allergy and What to Do About It.* By MILTON B. COHEN, M.D., and JUNE B. COHEN. Pp. 177; illustrated. Philadelphia: J. B. Lippincott Company, 1940. Price, \$1.50.

*Observations Made During the Epidemic of Measles on the Faroe Islands in the Year 1846.* By PETER LUDWIG PANUM, M.D. (Translated from the Danish by ADA SOMMERVILLE HATCHER), with a Biographical Memoir by JULIUS JACOB PETERSEN, M.D. (Translated from the Danish by JOSEPH DIMONT), and an Introduction by JAMES ANGUS DOULL, M.D. Pp. 111; illustrated. New York: Delta Omega Society, 1940. Distributed by The American Public Health Association. Price, \$2.50. (Review p. 546.)

*The Virus. Life's Enemy.* By KENNETH M. SMITH, F.R.S. Pp. 176; 1 illustration. New York: The Macmillan Company, 1940. Price, \$2.00.

*The Fundamentals of Nutrition.* By ESTELLE E. HAWLEY, Ph.D., and ESTHER E. MAURER-MAST, M.D., University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Including Table of 100-Calorie Portions by ESTELLE E. HAWLEY, ESTHER E. MAURER and HERBERT F. VAN EPPS, the Department of Vital Economics, University of Rochester, and Discussions of the Dietary Management in Specific Conditions. By Collaborators associated or formerly associated with The University of Rochester School of Medicine and Dentistry. With a Foreword by JOHN P. MURLIN, Ph.D., Sc.D., Professor of Physiology and Director of the Department of Vital Economics, University of Rochester. Pp. 477; illustrated. Springfield, Ill.: Charles C Thomas, 1940. Price, \$5.00.

*The Relativity of Reality.* Reflections on the Limitations of Thought and the Genesis of the Need of Causality. (Nervous and Mental Disease Monograph No. 66.) By RENÉ LAFORGUE. Translated by ANNE JOUARD. Pp. 92. New York: Nervous and Mental Disease Monographs 1940. Price, \$2.50.

*The Injured Back and Its Treatment.* Edited by JOHN D. ELLIS, M.D., with 7 Contributing Authors. Pp. 377; 17 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, \$5.50.

*The Chinese Way in Medicine.* By EDWARD H. HUME. Pp. 189; illustrated. Baltimore: The Johns Hopkins Press, 1940. Price, \$2.25.

*Progress in Medicine.* A Critical Review of the Last Hundred Years. By IAGO GALDSTON, M.D. With a Foreword by HENRY E. SIGERIST, M.D. Pp. 362. New York: Alfred A. Knopf, 1940. Price, \$3.00.

*The New International Clinics, Vol. 3, N.S. 3, 1940.* Edited by GEORGE MORRIS PIERSON, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. Pp. 358; illustrated. Philadelphia: J. B. Lippincott Company, 1940.

The 12 "clinics" in this number are from the Cornell Medical School; the progress review is on obstetric analgesia. Of the 9 "original contributions," E. R. Long's article on pneumatocele and Auerbach's on urogenital tuberculosis attract the reader's eye.

*Frank Howard Lahey. Birthday Volume, June 1, 1940.* Pp. 466; illustrated. Springfield, Ill.: Charles C Thomas, 1940.

*Modern Dermatology and Syphilology.* By S. WILLIAM BECKER, M.D., Associate Professor of Dermatology and Syphilology, Kuppenheimer Foundation, University of Chicago, and MAXIMILLIAN E. OBERMAYER, M.D., Assistant Professor of Dermatology and Syphilology, Kuppenheimer Foundation, University of Chicago. Pp. 871; 461 text illustrations and 32 full color plates. Philadelphia: J. B. Lippincott Company, 1940. Price, \$12.00.



The atrophy is best seen in the region of the clitoris where the preputial folds flatten out and the clitoris gradually disappears under the atrophic hood. The entire process is definitely limited to the non-hairy portion of the vulva and is sharply demarcated at the mucocutaneous junction with the vagina but it may extend posteriorly to involve the perineum and skin posterior to the anus. The final stage is a chronic one which lasts for years. The skin over the vulva becomes smooth, glistening, semitranslucent and parchment-like and its sharp demarcation from the adjoining skin is striking. The preputial folds and clitoris completely disappear. The labia majora and minora flatten out and disappear as separate structures but may still be identified near the urethra. The vaginal orifice is narrowed and even a gentle examination causes the skin to crack and superficial petechia to develop. Pruritus is the symptom which brings the patient to the physician and it is limited to the area involved by the disease. At first the itching may be intermittent but it soon becomes constant. It does not respond to the usual antipruritic lotions and it may keep the patient awake night after night until mental and physical exhaustion develops. The progress of the disease is slow, lasting for several years and there may be periods of remission during which the pruritus subsides. The likelihood that a carcinoma will develop can be lessened only by the removal of the chronically inflamed tissue which predisposes to malignant change. The authors believe that surgical removal of the vulva is the most satisfactory treatment for patients who have marked evidences of the disease. They have found the results of surgical treatment to be excellent. The patients are usually elderly women for whom marital relations are no longer important so that introital stenosis need not be considered. Careful removal of the vulvar tissues and suitable reconstruction will leave a useful vagina when this is important. Vulvectomy carries little risk even in the old and debilitated, for it is a superficial removal of tissue and can, if thought advisable, be carried out under local anesthesia. In their clinic palliative therapy has been discontinued since no suitable local therapy has been found. It is not sufficient to allay the pruritus but all sources of irritation should be removed, which can only be accomplished by removal of the involved skin.

While there is much confusion regarding the terms kraurosis, leukoplakia and pruritus vulvæ, Montgomery, Counsellor and Craig<sup>5</sup> state that they are usually distinguishable on clinical and pathologic grounds. In many cases all three may merge. Kraurosis is an atrophic process which may possibly lead to malignant change. Leukoplakia is a hypertrophic change, and definitely a precancerous dermatosis. Pruritus vulvæ with lichenification is a benign form of inflammatory dermatosis which *per se* does not result in malignant change. Resection of the pudendal, perineal or other nerves of the vulva is definitely contraindicated when malignant changes are either evident clinically or pathologically. In such cases vulvectomy is indicated. Resection of nerves should be avoided in the presence of psychoneurosis since even vulvectomy in these cases will be attended by many failures. Treatment with radium or Roentgen rays in cases of persistent vulvar pruritus due to any of the above conditions usually results only in temporary relief and if persisted in may lead to an actinodermatitis which may result in epithelioma of a relatively high grade of malignancy.

In the opinion of Swift,<sup>12</sup> leukoplakia, kraurosis, pruritus and atrophic vulvitis are due to a lack of absorption of vitamin A caused by a varying degree of achlorhydria. His experiences in Australia have shown that the addition of dilute hydrochloric acid to the normal diet of an Australian woman relieves the pruritus in the majority of cases with great improvement of the local vulvar condition. Vitamin A in the form of cod-liver oil should also be given. He feels that excision of the vulva should not be done except in those cases where there is a suspicion of malignant change.

If these changes are due to a loss of ovarian hormone it is only logical that replacement therapy with the use of follicular hormone should be tried. Rust<sup>9</sup> presents a summary of 65 patients with pruritus vulvæ who were treated by the use of progynon. Of this number, 48 (74%) were cured, 9 improved and in 8 patients the disease was not influenced by the treatment. Many of the patients had a severe form of the disease of long duration, in some instances of several years' standing which had resisted all other forms of treatment. If large doses of hormone are given, uterine bleeding is apt to follow as a result of hyperplasia of the endometrium caused by the hormone. This bleeding is never serious and can be controlled by reducing the dose or stopping treatment entirely. He feels that the results of this treatment are very satisfactory and preferable to such radical measures as chordotomy, nerve resection or vulvectomy.\*

Foss<sup>5</sup> has successfully treated 8 cases of kraurosis by the injection of massive doses of follicular hormone twice weekly. After the effect is obtained a gradual reduction in the dosage must be made. He has noted a marked improvement in the macroscopic appearance of the vulva with relief of dyspareunia.

Finkler and Marks<sup>3</sup> have administered estrogens to 50 patients presenting symptoms of this disease. In addition to the local symptoms most of their patients presented varying degrees of vasomotor and mental disturbances. The estrogens were administered by injection, inunction of the vulvar area, by suppository or orally. The effect of the therapy was checked by bio-assays, vaginal smear and endometrial and vaginal biopsy. They have found that the selection of the type of therapy to be used varies with the individual patient, depending upon the severity of symptoms, the local condition present, whether local or general symptoms predominate and upon the coöperation of the patient. Varying degrees of improvement resulted from all four methods of administration. The greatest relief from the general symptoms was obtained from intramuscular injections, while similar relief from oral administration could be obtained if used in adequate dosage. Most of the patients were considerably helped, although failure was observed in those patients who had complicating medical conditions such as diabetes, eczema, psychoneurosis or if the local vulvar disease was extensive. Mishell and Motylloff<sup>7</sup> have treated senile vulvovaginitis with local applications of estrogenic ointment and obtained results that they

\* The hormonal treatment is well worth trying. One of us (C. C. N.) has had marked success by employing Progynon-D II vaginal suppositories. The first suppository contains 4800 R.U. and is followed every other night with a suppository containing 480 R.U. After 11 suppositories have been employed there is usually marked improvement. The course may be repeated if necessary.

regard as striking. Estriol or trihydroxycestrin was chosen to be incorporated in the ointment base, as it has been fairly well established that this particular estrogenic substance is more easily absorbed from the gastro-intestinal tract than estrin or estradiol, and they felt that it might also be more easily absorbed through the skin. They found that the symptoms were usually relieved after 2 or 3 weeks and while recurrences may take place, they respond promptly to further treatments with the ointment. Systemic action following absorption of the hormone was evidenced by alleviation of the hot flushes so often associated with the menopause.

*The treatment of pruritus by alcohol injection* in 49 cases has been described by Wilson.<sup>15</sup> The patient is placed in the lithotomy position and the vulvar and perineal regions are prepared as they would be for surgical treatment except that shaving is not necessary. The exact areas of the vulva which are involved should be definitely marked on the skin. The patient will often point to the areas of the most intense itching and neglect to mention parts less involved. For this reason it is well to quiz the patient concerning the full extent of her annoyance, especially when the pruritus extends to the thighs, the buttocks or the abdominal wall, where characteristic changes in the skin are less prominent. The patient is then given a general anesthetic and 95% alcohol is injected by means of a 2 cc. hypodermic syringe which is calibrated in minims. The needle is inserted perpendicular to and through the skin so that the alcohol will be deposited just beneath the dermis in the subcutaneous connective tissue. An injection into the skin itself or too deeply into the subcutaneous tissues may produce a slough. Only from 2 to 4 minims of alcohol is injected at a single insertion of the needle. The number and the spacing of the injections depends on the extent of the pruritus, the age of the patient and the condition of her peripheral circulation, as well as the estimated efficiency of the circulation of the part to be injected. Elderly patients with arteriosclerosis or vulval and anal varicosities should be given injections cautiously, with a minimum of alcohol (not over 2 minims) at slightly wider intervals than younger women with efficient vascular systems. When the circulation seems unimpaired, one may inject as much as 4 minims of alcohol beneath every square centimeter of the involved skin. Immediately after the injection, the labia majora become edematous; the edema may reach its height in a few hours or perhaps in from 12 to 24 hours. After this time it slowly subsides so that after 3 to 10 days the vulva usually appears normal, though there is always a certain amount of subcutaneous induration in the region of the labia majora. This likewise subsides slowly, leaving in some cases a chain of small hard nodules, which disappear in from 4 to 6 weeks. The itching usually stops immediately, though occasionally one or two small areas of pruritus remain. These are usually areas that were overlooked or improperly treated, and they can be reinjected with the patient under local anesthesia if the itching persists after the edema subsides. As a rule this residual pruritus subsides in a few days or can be controlled with antipruritic ointments. Few patients complain of pain after alcohol injections. Although convalescence in the majority of cases amounts to little more than recovery from the anesthetic, Wilson always instructs patients to remain in bed for at least a few hours after the

injection. If the vulvar swelling becomes uncomfortable, hot moist dressings are applied. Some women resumed their usual occupation the day after injection, while others found it necessary to rest for 2 or 3 days. Wilson states that it is often surprising how rapidly the lesions heal after the injection. Excoriations, ulcerations, fissures, and so on, heal promptly and disappear in 10 days. The alcohol degenerates in the subcutaneous nerve fibers, producing a cutaneous anesthesia which persists until regeneration occurs. Probably more important are the changes in the vascular and the reticulo-endothelial system. There is a rapid mobilization of the neutrophils and histiocytes, which apparently dispose of the factors principally responsible for the pruritus as well as improving the cutaneous lesions.

**Malignant Tumors.** In discussing the incidence of malignancy of the vulva, Folsome<sup>4</sup> states that sarcoma of the vulva is rare, being either primary in the vulva or developing in the vulvar end of the round ligament. Its evolution is usually rapid, the lesion being irregular, nodular and covered with a thin layer of epidermis. It may resemble a fibroma until ulceration and infiltration take place. Once beyond local control these tumors may metastasize rapidly to most of the parenchymatous organs. Clinical experience indicates that radical vulvar surgery is the most successful treatment.\* Metastatic malignant tumors of the vulva in general are rare. As to the incidence of melanoma, Folsome has found but 3 cases in his records of 39 years or 1 case to each 125,000 pelvic examinations. These tumors are usually lobulated, bluish-black pigmented tumors which grow rapidly and metastasize very early to distant organs with early invasion of the lymph nodes. While the treatment of this condition is surgical, it is important to remember that the primary growth may appear small and readily operable long after widespread metastasis has occurred. Therefore, Roentgen ray examination of the chest, a careful history and physical examination to rule out distant metastases should always be a part of the preoperative program. The prognosis is extremely poor. Carcinoma of the vulva is the most common malignant neoplasm of the external female genitalia and is primarily a tumor of senility, being seen usually in the sixth or seventh decade. The three cardinal symptoms in Folsome's experience were pruritus (53%), soreness or actual pain (48%) and spotting or irritating leukorrheal discharge (28%). If one awaits the appearance of tumor mass, ulceration or actual edema of one or both lower extremities there is little hope for a favorable prognosis. No patient with pruritus vulvæ should be treated with indifference and the presence of any small tumor or ulcer of the vulva, irrespective of the age of the patient should be removed and examined microscopically. In Folsome's clinic treatment by irradiation either with or without operation has not been very satisfactory but the type and thoroughness of the operation is the most important factor. Extensive vulvar surgery with superficial and deep bilateral inguinal resection, commonly known as the Basset technique and as advised by Taussig, gives the best results.

The late results of treatment in a series of 74 cases of leukoplakic

\* In addition to radical vulvectomy and excision of the inguinal glands, Roentgen therapy is advisable.—C. C. N.

vulvitis and 112 cases of carcinoma of the vulva over a period of 30 years have been reported by Taussig.<sup>13</sup> He has found that leukoplakic vulvitis is permanently cured by vulvectomy in all but a few cases, although occasionally a secondary excision is required. The 5-year curability of 23 Basset operations for cancer of the vulva was 65 %, while the 10-year curability was 55 %. He believes that with an operability ratio of 75 % and a primary mortality of only 4.6 %, the surgical treatment of cancer of the vulva gives the most favorable prognosis of any form of malignancy of the genital tract except cancer of the uterine fundus. He emphasizes that radiation, vulvectomy and superficial gland operations have no place in the treatment of vulvar cancer except as palliative measures. Three out of 4 such cases should be subjected to the bilateral Basset gland excision with vulvectomy and approximately two-thirds of these will remain well for longer than 5 years.

In reporting a series of 118 cases of cancer of the vulva, Schreiner and Wehr<sup>11</sup> state that biopsy revealed epithelioma 115 times and adenocarcinoma 3 times. In their experience cancer may occur as a thickening of the epidermis which soon becomes cracked or fissured; as a warty or papillomatous growth which is primarily malignant; as a benign wart upon which the malignant process becomes ingrafted; or as an infiltrating type of growth which soon ulcerates, giving rise to bloody or purulent discharge or pain. As to treatment, they feel that the only hope of eradicating vulvar cancer is by its early recognition and radical destruction by coagulation plus heavily filtered irradiation. Where the disease apparently was local, 42 % *lived* 5 years or more under such treatment, while 31.5 % were *free from disease* for a period of 5 years or more. However, a 5-year cure is very exceptional if there is metastasis in the groins.

From his experiences with irradiation at the Memorial Hospital, Healy<sup>6</sup> has found that the normal tissues of the vulva will not tolerate the necessary radiation dosage. Where attempted, it has resulted in prolonged and extensive ulceration and slough, causing much destruction of normal tissues, great suffering and in many instances has probably shortened the patient's life. Attempts have been made to carry out preoperative irradiation of the lesion with radium and of the groins with Roentgen ray and, at a subsequent date, to do bilateral groin dissection and complete vulvectomy. Such attempts have been complicated by the damage resulting from irradiation and have in many instances delayed or prevented the possibility of operation. They have done a large number of complete vulvectomies at the Memorial Hospital with either single or bilateral groin dissection and have been impressed by the few cases in which enlarged palpable glands were involved by cancer, the vast majority of cases being merely inflammatory. Therefore, they have omitted radiation entirely in the treatment of the primary lesion. They do a complete vulvectomy, extending out to but not including the groins or the femoral regions. The groins are irradiated with a full dose of high voltage Roentgen ray during convalescence from the operation and thereafter are closely observed, and if any suspicious nodes make their appearance, they are exposed under local anesthesia, and radon gold filtered seeds are inserted in an amount equivalent to not less than 5 skin erythema doses to the area treated. By this procedure the primary lesion has been completely cured and

the use of interstitial radiation in the inguinal nodes not only takes care of the node but also of the surrounding gland bed.

**Bartholin's Gland.** In discussing tuberculosis of Bartholin's gland, Schaefer<sup>10</sup> states that the disease occurs as a chronic, usually non-painful, indurated swelling in which there are no signs of an acute inflammation. If the duct is patent, there may be a glairy, mucoid, brown or colorless discharge. The abscess never reaches a large size and is seldom more than 2 cm. in diameter. Incision of the gland results in a persistent draining wound. Only 8 cases, including the one which he reports, have thus far been described—all unilateral. He believes that more cases would be found if most physicians did not regard every case of Bartholinitis as gonorrheal, or if these glands were more frequently examined at operation or autopsy and if all tuberculosis institutions had a gynecologic service. It is important to demonstrate the cause of a Bartholinitis, not only to treat the gonorrhea if present, but also, if tuberculous, that other tuberculous foci, whether they be pulmonary, osseous or genito-urinary may be looked for. The most common route of infection of Bartholin's gland by tuberculosis is from a positive sputum, but it may arise from vaginal or cervical tuberculous ulcers, from the blood or lymph stream, and from the gastro-intestinal or urinary tract. The treatment of the condition consists of wide excision of the gland and its duct and closure of the wound without drainage.

Duncan<sup>2</sup> reports what he believes is the first case of endometrioma of Bartholin's gland. The patient complained of a hard painful mass on the left side of the vulva which had caused trouble for a year and a half. The pain became worse at each menstrual period and decreased after the flow stopped. Four years before the present admission she had had an acute inflammation of the gland, at which time it was incised and drained. The day following operation she began to menstruate. On examination, a firm bluish nodule, 2 cm. in diameter, was found at the site of the left gland and a diagnosis of endometriosis was made. The removed tumor presented the typical picture of endometriosis microscopically. Duncan believes that following the incision and drainage menstrual blood containing living endometrial cells penetrated the site of the gland and produced the tumor.

**Elephantiasis.** In presenting his study of 26 cases of elephantiasis of the vulva which were seen in the Charity Hospital in New Orleans, Witherspoon<sup>16</sup> states that this disease is a clinical and pathologic entity in which the essential pathologic change is not so much an edema from lymph stasis as a fibromatosis or hypertrophy of the underlying connective tissue. While lymph stasis is an essential step in the development of the disease and can be caused by any type of trauma or infiltration, the hypertrophic changes of the underlying connective tissue cannot occur until another factor, generally accepted as an infection of some sort, has been superimposed. The streptococcus is the commonest infecting agent, but any other organism might be responsible. The intermediate step of infection is necessary even in the type of elephantiasis caused by filariae or other parasites. Elephantiasis of the vulva is usually caused by syphilis. The cases in this series were all in colored women, the majority of whom were in their twenties or early thirties. In nearly three-fourths of the cases clinical or serologic

syphilis could be demonstrated and in practically the same number ulceration was a factor, the portal of entry for infection thus being clear. Vulvectomy was performed on 20 cases, 2 of the remainder being poor risks, while the other 4 refused operation. A more or less complete vulvectomy was necessary in all cases. Two died, a 10% mortality, 1 from myocarditis and the other from pelvic peritonitis. Malignancy was not a factor in any case, an interesting observation, as chronic irritation is a notable feature of the disease.

**Granuloma Venereum.** An interesting report on the disease known as granuloma venereum (inguinale) has been presented by Wolfe and Tortora.<sup>17</sup> This condition is a chronic inflammatory disease of disputed venereal origin, characterized by ulcerating lesions of the skin and mucous membrane of the genito-inguinal regions and histologically by the presence of Donovan bodies in the monocytic cells of the exudate. The disease is extremely chronic and shows no tendency to spontaneous healing. It usually affects the external genitalia and perianal regions and often invades the vagina but rarely affects the cervix. The period of incubation varies from a few days to several months. There are rarely any constitutional symptoms and there is little local pain aside from burning and itching. It usually is seen in adult negroes and is thought to be transmitted by sexual contact. The lesions appear either as nodular elevations with serpiginous ulceration or as hypertrophic and keloid lesions. In the later stages secondary infection may occur and constitutional symptoms appear. Histologically, the pathognomonic cell is a relatively large monocyte 25 to 90 microns in diameter containing deeply staining bodies varying in size from 0.5 to 2 microns. The diagnosis may be difficult in spite of these characteristic cells, but the response to arsenical therapy is also helpful.

The disease is often confused with lymphogranuloma inguinale or lymphopathia venereum which is a disease of the lymphatic channels and lymph nodes, while granuloma inguinale is a disease of the skin and subcutaneous tissues. The primary lesion in lymphogranuloma inguinale is rarely encountered on the external genitalia; usually the vagina and cervix are the primary seats. The initial lesion heals quickly so that it is seldom found, while the enlargement and suppuration of the inguinal lymph nodes is frequently the first finding. In late cases a stricture of the rectum is encountered. The positive cutaneous response to injected antigen from suppurating lymph nodes (Frei test) is specific for lymphogranuloma inguinale while Donovan bodies are lacking. In the treatment of granuloma venereum Wolfe and Tortora advise tartar emetic given intravenously, beginning with 2 cc. of a 1% solution in distilled water and slowly increasing the dose until 10 cc. is reached. Injections are given every second or third day and continued weekly for 2 or 3 months after healing has occurred, in order to prevent local recurrences. Not more than 30 injections should be given in one course. Recently a new antimony drug called "fuadin" has become available and may be used intramuscularly. In rare cases where antimony is contraindicated or produces no results, surgery, Roentgen ray or coagulation must be resorted to.

**Imperforate Hymen.** A curious fact which has been brought out by Tompkins<sup>14</sup> in his excellent review of the subject of imperforate hymen with hematocolpos, is that the condition is seldom diagnosed by the

physician who first sees the case. Amenorrhea is seldom offered as a complaint. The patient's mother generally assumes that her daughter is slow in maturing and does not associate the abdominal pain which is present with failure of the menses to appear. The pain is usually poorly localized in the lower abdomen and is typically dull and intermittent rather than severe and constant. These qualities together with the history of attacks "about a month apart" often suggest recurrent appendicitis and may lead to an unnecessary laparotomy. A very common symptom is inability to void or at least difficulty in voiding. Severe pain is almost always due to overdistention of the bladder. Tompkins states that an imperforate hymen should always be suspected when an adolescent girl who has not menstruated complains of disturbance referable to the bladder. In addition to the foregoing symptoms there may be abdominal enlargement, a protruding mass at the vulva or pain on sitting. While an imperforate hymen may be found at any age, it is most commonly discovered between the ages of 11 and 18 when obstruction to menstruation begins to produce symptoms. The diagnosis can be made at once by inspection. While several plans of treatment for this condition have been suggested, the chief complication of any of the procedures is ascending infection leading to pelvic inflammatory disease, peritonitis or death. Old blood is an excellent culture medium, and once infection enters the vagina the dilated cervix, uterus and tubes offer no resistance to its ascent. The plan of treatment which Tompkins recommends begins with meticulous preoperative preparation of the vulva and perineum. The hymen is completely excised, not simply incised and no vaginal examination is made at the time of operation. After evacuation of the retained blood from the vagina on the operating table, a careful rectal examination to determine whether there is distention of the tubes should be made. If there is evidence of hematosalpinx, laparotomy should be performed and the tubes incised and drained or, if necessary, removed. A postoperative dressing of gauze soaked in bichloride of mercury should be applied to the vulva and the patient placed in high Fowler position to promote drainage. Enough morphine should be given to produce constipation for 4 days after operation and the perineum should be carefully cleansed after every evacuation. The patient should remain in bed at least 1 week after the temperature is normal. There should be no tub bath or douching until two menstrual periods have occurred.

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## DERMATOLOGY AND SYPHILOLOGY.

UNDER THE CHARGE OF

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CONTROL OF SYPHILIS, UNIVERSITY OF PENNSYLVANIA.THE PSYCHONEUROGENOUS COMPONENT OF CUTANEOUS  
REACTION MECHANISMS (PART II).

THE following material is the concluding portion of a review begun in October, 1939 (*Am. J. Med. Sci.*, 198, 577). In the conclusion it is proposed to give a list of the dermatologic conditions in which psychoneurogenous components have been clearly recognized. In the compiling of such a list, it should be recalled that psychogenous and neurogenous factors may be imported incidentally into the general clinical picture of which a dermatosis is a major or minor part, as concomitants, rather than influences of etiologic importance. Thus the extraordinary scabrous activity with accompanying dermatitis observed by Haxthausen<sup>33a</sup> in cases of encephalitis, is interpreted by him as a concomitant of inflammatory injury to the thalamic fat control center. The mental state of the encephalitic in general can hardly be regarded under such circumstances as of primary causative significance. Scleroderma (by which is apparently meant the acrosclerotic syndrome, rather than the morpheic type) (Sellei<sup>60</sup>) is by some authors rated as of neurogenic causation, because an extended literature has demonstrated the widespread nerve injuries both central and peripheral, accompanying this type of disturbance. The depressed mental state of the victim is an inescapable element in the clinical whole, but it is a question whether the psychic factors involved play a primary or a secondary rôle. In the clinical observation of such patients, psyche and soma often seem rather to be involved in a vicious circle, in which physical malfunction leads to depression and depression in its turn to even more exaggerated physical malfunction. The question also arises as to just where one should place the trophoneurodermatoses such as the chronic unilateral dermatitis of the face described by Becker,<sup>7a</sup> Herrick,<sup>34</sup> Netherton<sup>49</sup> and others (*cf.* Loveman<sup>45</sup>), as an accompaniment of gasserian ganglion extirpation or destruction. Zosteriform eruptions associated with infective injury or malignant cell infiltration of cranial or spinal nerve sensory ganglia are neurogenic perhaps in much the same sense.

The multiplicity of causes which characterize the mechanisms operating in the production of many skin diseases also obstructs listing. The interaction of emotional and allergic factors and the infection-

allergic complexes alone greatly increase the difficulty of giving an exact rating to the psychoneurogenous in the eczema-asthma-hay fever complex (prurigo Besnier); in dyshidrosis (infective-allergic conditions of the hands and feet); rosacea and the "flush" dermatoses and so forth. The interplay between infection and contact allergy on the one side, and the nervous control of perspiration and circulation on the other, make it extremely difficult to decide at what point the seemingly vicious circle begins or ends. It is clear, then, that classification will probably be even more difficult than listing.

Rogerson,<sup>66b</sup> in listing the dermatoses in which the psychologic factor can be recognized, places erythema, dermatographism, urticaria, eczema, pruritus, prurigo (Besnier) (the eczema-asthma-hay fever complex), alopecia areata, vitiligo, scleroderma, dyshidrosis and neurotic excoriations (self-inflicted eruptions) in his major classification, and places herpes simplex, lichen planus and psoriasis in a group in which emotional disturbances are only occasionally seen to be of etiologic importance.

Becker,<sup>7b</sup> from a study of the physical and mental backgrounds of patients with neurovascular instability, as he designates it, lists the following as functional dermatoses which may properly be spoken of as "neurodermatoses"; idiopathic pruritus, generalized and localized; neurotic excoriations, neurodermatitis (dry and exudative types), dyshidrosis, idiopathic chronic urticaria, and angioneurotic edema, alopecia areata, totalis and universalis, lichen planus, vitiligo, rosacea.

The following is a discussion based on attempted classification.

**Disorders Affecting Hair and Pigment** (alopecia totalis, alopecia areata, vitiligo, pigment anomalies, trichotillomania). Beeson and Pickett<sup>8</sup> have furnished the most recent summary in the American literature on the causative background of geographic and total hair-loss, based primarily upon repetition of the experimental work of Max Joseph.<sup>38</sup> Genner,<sup>25</sup> 4 years earlier, admirably summarized current clinical knowledge in a monograph on pelade in which he classified alopecias of the island type into three groups: the first due to peripheral nerve injury, especially in the neck; the second due to general disease of the nervous system; and the third to emotional shock. The experimental work on cats performed by Joseph and repeated by Beeson and Pickett, with alopecia developing at varying intervals following nerve resection in approximately 33% of cases has been subjected to a thorough-going control critique by Aubrun.<sup>4</sup> By covering with a leather cap the areas about the heads of his cats, in which "alopecia" and "trophic" lesions usually developed, Aubrun was apparently able to show that "neurogenic" alopecia may be an artefact produced by the cats' scratching of itching and hyperaesthetic areas. The traumatic factor apparently looms large in what had previously been accepted as an experimental demonstration of true trophoneurotic origin. Wright,<sup>67</sup> as the result of cervical plexus resection in man, could find no evidence for the trophoneurotic origin of alopecia areata. Over against this inconclusive experimental material must be set a gradually increasing accumulation of individual cases in man, in which nervous shock has been followed by total or partial hair-loss. Wright has suggested as the result of his negative experiences in the experimental field, that the underlying mechanism of alopecia areata is vasomotor or circulatory rather than neurogenic,

as such. The suggested instrumentality of endocrine disturbance rests on such slender evidence as hair-loss or hair-growth conditioned by pregnancy or associated with thyroid disturbances.

The association between hair-loss and hair-depigmentation is clinically familiar. Genner,<sup>25</sup> Brown<sup>16</sup> and Roxburgh<sup>57</sup> believe that there may be neurogenic factors in vitiligo. Ramel,<sup>53</sup> in a rather loosely hung discussion, includes both depigmentation and hyperpigmentation among these trophoneuroses. Klauder,<sup>42a</sup> examining the question of sudden loss of hair and sudden turning white of the hair, finds many of the cases to be apochryphal and the most recent credible account to be that of Vignolo-Lutati<sup>64</sup> (1918) in connection with war shock and so forth. Goodman<sup>29</sup> has made the interesting suggestion that the pattern baldness over the temples and that over the tonsure area has a distinct trophoneurotic background, dependent on the age of the individual. He points out that in the preadolescent, thallium acetate produces a hair-fall over the entire scalp, whereas in the adult only the hair of the tonsural area falls.

Trichotillomania is not a trophoneurosis, but a habit spasm or tic, with a definite psychogenous background. The pulling out of the hair and the breaking off of hairs (trichokryptomania) produces patterns easily confused with other geographic types of alopecia, and the nervous tension and conflict developed by parental repressive influences, school stresses, hysteria and compulsion neurosis are usually not apparent until several consultations have been had. Most of the victims are adolescents, and Klauder credits mass suggestion that epidemics of the disturbance observed in boarding schools and so forth are due to mass hysteria. Alkiewicz<sup>1</sup> has reported a case of picking off of the nails, which evidently belongs in the same group of conditions.

**The Self-inflicted Lesions of the Skin** (factitial dermatoses, dermatitis artefacta). The more or less standard presentations of this subject including those of MacKee<sup>47</sup> and Stokes and Garner<sup>61f</sup> have been supplemented since 1929 by analyses of individual cases emphasizing psychical factors, such as that of Gillespie;<sup>26a</sup> Saegesser's<sup>59</sup> very interesting discussion of leg ulcers in which it appears that a psychic stigmatization factor necessitating attention to the mental state of the patient is operative; and Rogerson's<sup>56b</sup> case suggesting that occupational contacts and neurogenic factors may be interwoven in the background. Gillespie emphasizes the diagnostic importance in identifying the hysteria factor in self-inflicted dermatoses, of the appearance of hysterical paralyses. He differentiates the true hysterical cases from the more commonplace examples of malingering, attention-getting and similar motivations. He believes that hysterics in general may not know *why* they produce signs and symptoms of illness, but that many more are aware that they do actually produce them than is commonly believed. The patient thus inflicts the lesion in full consciousness of everything but the motive back of the act. Gillespie even believes that the amnesia with respect to motives may be an artefact and the result of self-deception afterwards, the patient lying in self-defense and then coming to believe his own tergiversation. The domination by a fixed idea may proceed to the point of permitting amputation, though the amputation is not proof positive of hysterical origin, and may occur as part of a compulsion neurosis.

Haxthausen concludes that hysterical lesions of the skin are purely of external traumatic origin, and belong to the group appropriately labeled "pathomimia." He finds no evidence that the skin of hysterical individuals reacts with abnormal severity towards external irritation; but Bettmann,<sup>9</sup> Rasch<sup>51</sup> and other older writers maintain the contrary. Haxthausen,<sup>33b</sup> by a series of experimental studies, apparently demonstrated that there is no intrinsic difference between the reactivity to trauma of hysterical and normal skin, though he concedes that the attempt at evaluation of the experimental trauma may be conditioned by the hyper- or hyp-esthesia frequently noted in hysterics.

MacCormac's<sup>46</sup> recent presentation of so-called "autophytic dermatitis" gives a useful classification into: 1, *purposeless hysterical eruptions*, almost exclusively confined to young unmarried women; 2, *Purposeful and hysterical eruptions*, occurring in women of mature age who attempt to evade unwelcome duties. This is the malingering group in which monetary or other gains, or the avoidance of disagreeable duties is obvious; 3, *the mischief group* in which children desire to mystify their elders; and 4, *phantom dermatosis*, in which the patient complains of a dermatologic condition which he considers obvious and disfiguring but of which no traces can be found by an unprejudiced observer. MacCormac gives an interesting prognostic note regarding 11 young women followed over a period of years, all but 1 of whom ceased to inflict lesions on the skin and entirely forgot their previously conscious acts.

Gillespie gives the most recent classification of motives in self-inflicted skin lesions as follows: 1, dermatitis artefacta as a "dodging reaction," for the avoidance of some difficulty; 2, as an attention-getting device; 3, as part of an hysterical syndrome; 4, as a symptom of a compulsion psychoneurosis; 5, as a mode of exhibitionism. Cases illustrating each type are given. Gossip,<sup>30</sup> in discussing vicarious menstruation, points out its relation to hysterico-epilepsy. He believes that the hysterical factor outweighs ovarian endocrine influences, prepuberal maladjustments and menstrual irregularities. Brown,<sup>14</sup> in presenting what he believes is the first case of dermatitis artefacta treated by psychoanalysis, quotes Prosser-Thomas<sup>52</sup> as calling particular attention to the favorable significance of anxiety and depression developing in the hysteric as he becomes aware of the nature of his acts of self-infliction. Brown's psychoanalysis of his patient, which resulted in the permanent cure of the patient's ulcers, attached the mental process to a masturbation episode and masochistic scratches. Saegesser's<sup>59</sup> very interesting study of leg ulcers in a young woman gives a number of reasons for his belief that her introspective contemplation of the ulcer and its intimate association with unhappy episodes was a factor in maintaining the pathologic condition which was only overcome by distracting her attention from the lesion, and concealing it from sight. Apparently no outright self-infliction was involved. Rogerson's<sup>56b</sup> case, combining occupational and neurogenous factors, occurred in a worker who developed a cement dermatitis of the hands which improved but did not clear on occlusive dressings and elimination of the occupational factor. The anxiety element was conspicuous until a complete change in his psychologic outlook took place with the awarding of adequate compensation. Thereupon the dermatitis disappeared. Cases such as these,

if a sufficient number accumulates, will tend to support via the vasomotor mechanism in all probability, the belief supported by Klauder<sup>42b</sup> in his discussion of stigmatization, that psychic processes are able to affect the localization as well as the severity of cutaneous lesions.

**Erythema-Urticaria Group** (including vasomotor neuroses). Under this title there are included by various authors the cutaneous edema phenomena of dermatographism, urticaria and angioneurotic edema, conditions associated with angiospasm, including Raynaud's disease, acrosclerosis and scleroderma, the "flush" dermatoses, including rosacea and erythromelalgia; and hemorrhagic (stigmatization) phenomena. In connection with the urticarias especially, mention has already been made of the cholinergic type whose mechanism is described in the previous review. Urticaria associated with sexual relations is not unfamiliar and Dunbar<sup>21</sup> has rather startlingly analyzed a case in which a young woman spontaneously developed urticaria as a method of compromise, so to speak, between the desire of her sadistic partner to raise welts on her with a belt, and her feeling that she should dismiss him, though she ardently desired to retain his attentions. By raising her own "welts," she retained her partner and avoided the beating. When the mechanism was explained the urticaria disappeared. Stokes, Kulchar and Pillsbury<sup>61a</sup> give some rather interesting figures as to the importance of the psychoneurogenous factor in the multiple etiology of chronic urticaria. A psychoneurogenous factor was present, plus other causes in 68% of cases. Psychoneurogenous factors were the sole recognizable cause in 12% of cases, and no psychoneurogenous factor could be recognized in 17% of cases. Nine cases are cited with various types of precipitating incidents and response to a psychic reëducation technique. Urticariogenic response seems to have familial or even hereditary background, and to be based on what Stokes<sup>61c</sup> subsequently called the "tension frame of mind." Rogerson<sup>66a</sup> adds to the accumulating evidence that urticaria produced by physical allergens can be influenced by psychic factors, the case of a boy allergic to fish and Brazil nuts whose allergic symptoms disappeared when in a happy frame of mind.

Rosacea and congestive conditions of the flush areas were connected with the psychogenous influence of the slow-acting long-time chronic wear-and-tear type by Stokes and Beerman.<sup>61e</sup> The very important influence of guilt and anxiety, summarized by Klaber and Wittkower<sup>41</sup> under the term "social anxiety" in the etiologic background of rosacea, has recently been strongly supported by their special studies. The flushing of the center face, on which develop acneiform eruptions, exaggerated seborrheic processes and so forth, was in 36 of their 50 cases apparently the direct result of acute psychologic trauma, and in a further 20 cases, of a preceding prolonged social or sexual stress. The vascular congestive base of the process is linked with Harmer and Harris<sup>71</sup> observations on the similarity of the rosacea syndrome to that induced by the injection of histamine. This possibility is also invoked by Stokes and Beerman, the histamine-like substances being absorbed as the result of gastro-intestinal abnormalities developing in the rosacea type of patient.

**The Angioneuroses, Angiospasm, Erythromelalgia.** Surprisingly little attention has been given in recent years to the psychoneurogenous background of the vasomotor neuroses. Vorhees<sup>65</sup> pointed out the effect

of worry, excitement in producing paroxysms, and the influence of nervous states on "dead finger," acrocyanosis and so forth, seems tacitly accepted without an adequate analytical study. Erythromelalgia has had practically no critical examination from the standpoint of psychoneurogenous factors in even such an extended report as that of G. E. Brown<sup>15</sup> from the experience of The Mayo Clinic. This silence on the matter is the more interesting in the light of the report of Mumford on a case of monolateral erythromelalgia, apparently of hysterical origin, cured by suggestion. The observations of Hartson<sup>22</sup> on so-called stocking erythrodermia afford interesting linkage between the pure vasomotor neuroses of the extremities and those vasomotor disturbances which underlie the development of actual dermatitis of the hands, legs and feet. O'Donovan<sup>50</sup> deserves credit for insistent emphasis on the importance of psychoneurogenous factors in conditions of this sort.

**Vagus-Sympathetic Imbalance.** Brill's<sup>13</sup> observations on the preponderantly vagotonic background of the neurodermitides, have been followed by Rogerson's endorsement of the importance of vagus-sympathetic imbalance with emphasis on the vagotonic type of disturbance, as characteristic of prurigo (Besnier) and the eczema-asthma-hay fever complex. Rogerson<sup>56b</sup> quotes, as worthy of extended emphasis, the clinical characteristics both of the skin and other structural systems, predicated by Eppinger and Hess,<sup>24</sup> for the vagotonic and sympathicotonic types.

#### *The Vagotonic Type.*

- A. Exemplified by the person with the asthma-eczema-prurigo syndrome.
- B. Psychologically usually introvert.
- C. Cutaneous characteristics: complexion sallow with an earthy tint; lips bluish; skin appears thickened and harsh; tends to be edematous owing to the retention of fluid in it: marked tendency to hyperpigmentation, particularly in the areas of the prurigo; white dermatographism; scratching and rubbing result in lichenification; hyperhidrosis of the extremities may be present, but skin as a whole is dry and often ichthyotic. Response to anger: pallor.
- D. Vascular system: blood pressure tends to be low, particularly when exhaustion of the adrenal sympathetic system occurs after nerve strain or acute infection; with fall of blood pressure increased pigmentation is likely to appear. There is often circulatory stasis in the extremities so that hands are bluish and cold to touch. Erythrocyanosis of the legs is common in females. Capillaries fill slowly after obliteration by pressure. Pulse rate tends to be slow and temperature to be subnormal.
- E. Tolerance to adrenalin and thyroid extract high.

#### *The Hypersympathicotonic Type.*

- A. Exemplified by the person with established or potential Graves' disease.
- B. Psychologically usually extrovert.
- C. Cutaneous characteristics: skin usually white, thin and transparent, with marked tendency to flushing (erythema); lips bright red; vitiligo rather than diffuse pigmentation common; also alopecia areata and scleroderma; red dermatographism often with whealing; lichenification rare; generalized hyperhidrosis common. Response to anger: flushing.
- D. Vascular system: blood pressure likely to fluctuate, temporarily high in states of emotion and excitement. Peripheral circulation usually good and extremities warm but Raynaud's disease may occur. Capillaries fill quickly after obliteration by pressure. Pulse rate tends to be rapid, and the heart beat tumultuous. Temperature is normal and may be raised in state of emotion.
- E. Tolerance to adrenalin and thyroid extract low.

Szondi<sup>63</sup> and, more recently, Becker have pointed out that pure cutaneous vagotonia and hypersympathicotonia rarely exist, and that both are essentially structural or local neural disturbances, so that a hypersympathicotonic skin may be accompanied by vagotonic gastro-intestinal tract and so forth. Becker has developed the term "neurocirculatory instability," as covering both types of conditions, and as descriptive of the type of patient who tends to develop the dermatoneuroses. It is at once apparent to students of this problem that the proportion of psychoneurogenous influence in all of these conditions varies not only quantitatively, but qualitatively, and that it is therefore hazardous to propose outright an inclusive list of neurodermatoses, and preferable to speak of the psychoneurogenous components in this, that, or the other dermatosis.

The Besnier prurigo or eczema of the eczema-asthma-hay fever complex, conforms in clinical experience so closely to the vagotonic type of cutaneous disturbance and has such distinct entity characteristics, that the work of the Gillespie-Guy's Hospital group including Rogerson and Strauss, on the psychogenous background of the eczema-asthma-hay fever complex should be summarized here:

Based upon Rogerson's<sup>56</sup> studies of the material of the asthma clinic of Guy's Hospital and the observations of Stokes<sup>61d</sup> and others on the adult personality, the psychologic background of the eczema-asthma-hay fever complex may be summarized as follows:

1. A deep-seated feeling of insecurity.
2. An easily developed feeling of inferiority.
3. Aggressiveness; disposition to dominate, demand attention; a species of drive, possibly compensatory for (1) and (2), but also including an element of—
4. An intense self-consciousness, or I-sensitiveness, the "Liebe Ich" or "Beloved I" of the German literature. This is less a vulgar and robust egotism than it is a kind of ultrasensitiveness, like hypersensitiveness to physical pain.
5. Marked lability of physical and mental reactions, which in some becomes adaptability and in others instability.
6. An intrinsic kinetic drive, a species of thalamic pressure, which is probably interwoven with or causative of (3) and which is at the bottom of—
7. An all-or-none type of reactivity, a species of spark-over which knows no half-way or compromise approaches to problems, or reactions to stimuli (with spasmophilia as a physical expression?), plus—
8. A higher-than-average intelligence quotient, plus—
9. Tension, expressed or repressed.
10. A restlessness which is not instability, but is due to the rapid exploration and exhaustion of a subject, a problem or a possibility by a high-pressure mind of exceptional capacity. The constant exhaustion of the possibilities of the moment or the situation, leads to boredom and flight rather than exhaustion and rest.
11. A deep-seated over-dependence, product of (1) and (2) with traces of (3) and (4).
12. A special reactivity to competition, human and personal, possibly a product of (1), (3) and (4).

The work of Rogerson and Strauss<sup>55c</sup> in clearing the Southampton Asthma Retreat of Guy's Hospital of patients who now largely carry on in complete freedom or greatly improved status at home, through the application of psychotherapy directed at the above-described background, is the best testimony available to the significance of the psychologic element in this group of cutaneous conditions.

**Inflammation (dermatitis and eczema).** It is again fundamentally necessary in reviewing psychoneurogenous components in inflammatory disease of the skin, to keep constantly before one the etiologic complexity underlying regional and general dermatitic eruptions. Where the causative mechanism may and constantly does involve elements of insufficient or disturbed physiologic defense (ichthyosis, seborrhea); various forms of allergic disturbance due to inhalant, ingestant and contact agents; various infective elements (fungi, pyogens especially); light sensitiveness due to local or systemic conditions, it must be clear that the psychoneurogenous element, operating as it probably does, largely through vasomotor and sweat disturbances quite apart from any supposed distinctive "trophoneurotic" mechanism, must be very conservatively interpreted in order to avoid the grossest forms of "post hoc-ism." One of the best series of case descriptions evidently involving psychoneurogenous factors without necessarily a clear-cut placement of this element in the etiologic complex, is that of Klauder. This presentation is typical of a number in the literature in which the psychoneurogenous factor in the background is clearly present, but the instrumentality through which it operates is either not completely investigated, or is otherwise not adequately defined. Much of the available information in the literature is in precisely this state of inadequate definition. Here and there individual items, particularly involving the allergic state, have been clarified by responses or cures obtained under hypnosis or illuminated by experimental studies such as those of Diehl and Heinichen,<sup>20</sup> but the relative proportion of established and presumed connection is still much too large on the presumptive side. In the case of neurodermatitis and the flexural eczemas, interesting connections with such phenomena as histamine intoxication are developing. It is clear that histamine intoxication is accompanied by a mental state comparable to that of the depression of many neurodermitides; and similarly it is clear that histamine when injected intramuscularly can give rise to an increased skin temperature conforming in distribution characteristics to the clinical picture of neurodermatitis (Williams<sup>66</sup>). Reference has already been made to the emotionally controlled apocrine sweat mechanism, and its relation to flexural mycoses and streptomycoses (Darier-Ravaut-Ramel syndrome<sup>55</sup>). The so-called dyshidroses (dermatitic or eczematoid eruptions of the hands) probably provide at this moment the clearest illustration of the importance of psychogenic factors in the complex of allergic-infective dermatitis that we have available. Hartson, mentioned above, as long ago as 1929 reported a series of so-called stocking erythrodermias, of which O'Donovan also had cited cases which he regarded as a clinical entity in which he believes the psychogenic factor was so important as to justify classification with the neurodermitides. Treatment in these cases, however, suggests that such factors as mild venous stasis had not too fully been considered. Becker cites several case histories, in



which the etiologic work-up however can scarcely be regarded as complete. The approaches from the psychiatric side have also not taken too seriously the necessity for a comprehensive etiologic study in these cases. Bartemeier's<sup>6</sup> review of the literature including the cases of Jelliffe and Evans<sup>37</sup> (psoriasis as an hysterical conversion symbolization), Allendy<sup>2</sup> (eczema of the hands), Barinbaum<sup>5</sup> (eczema of the fingers, 1 case; inguinal intertrigo, 1 case) all appeared to lack comprehensive study from the standpoint of infection-allergic factors, among others. Bartemeier's own case of a 25-year-old Jewish dental student with a patch of dermatitis on the dorsa of the hands, cured with 2 years' complete freedom from relapse, by psychoanalysis, approaches more nearly at least a demonstration of the influence of the psychogenic in these cases.

Barber, the head of the Dermatological Clinic at Guy's Hospital, and Gillespie (case reported by the latter) described a case in which they believed that the use of the hands in the occupation is what determines the expression of dissatisfaction by a skin lesion of the hands, rather than some other organ. This is particularly discussed as significant in certain types of occupational dermatitis (Rogerson's case of cement worker already referred to). Kelman and Field<sup>40</sup> describe a case which illustrates quite strikingly the succession of contact and other allergic accidents, intercurrent infective predisposing elements and so forth, which may interact with the psychogenous background of certain types of patients. An even better case is that reported by Pearson<sup>51</sup> of dyshidrotic eruption of the hands and feet cured by psychoanalysis and psychotherapy after the complete failure of thoroughgoing and careful topical and systemic treatment for the allergic-infective elements. This patient, who suffered immediate exacerbation of her eruption under even such relatively minor stimuli as waiting in the office, was found to be the victim of a conflict similar to that which was responsible for Gillespie's<sup>26b</sup> case of excessive sweating. Adjustment of the conflict led to a complete and lasting recovery.

**Trophoneuroses.** It is proposed here only to mention such cases as that of Becker's woman patient with unilateral dermatitis of the face, and gingivitis, developing after the removal of the gasserian ganglion. The literature includes besides the older cases, recent reports by Herick,<sup>34</sup> Netherton,<sup>49</sup> and Loveman.<sup>45</sup> The instrumentality of the Lewis-Dale or antidromic nerve impulse mechanism deserves consideration here.

**Disorders of the Sweat Mechanism.** Dermatoses ascribable to abnormality in the nervous control of sweat were discussed in as great detail as the literature permits in the preceding section of this review. It should be recalled that the apocrine sweat glands are known to secrete odoriferous substances which may be responsible for bromidrosis, but the complexity of the bromidrosis problem is well illustrated by a recent summary (*J. Am. Med. Assn.*, 112, 1408, 1939).

**Pruritus.** The recent physiology of the itch mechanism is dealt with in the preceding section of this review. The current neuropsychiatric contributions concern mainly the sex or erotic elements in pruritus. Generalized itching associated with extensive dermatitis or eczema, and with neurodermatitis, and pruritus without obvious cutaneous lesions

have been described with attendant circumstances suggesting masochism and cutaneous masturbation by several authors including Stokes.<sup>61a</sup> Klauder has on various occasions expressed the belief that such relations can be overemphasized. Rogerson's recent review, however, cites in detail Cornia and Slight's<sup>19b</sup> case, which seems inescapably one of scratch substitution in an unsatisfactory sexual relationship. Gillespie described a case of general prurigo with severe cutaneous masturbation accompaniment. *Pruritus ani et vulvæ* seem to be more clearly recognized as having sexual components. Hunt,<sup>35</sup> however, in 300 cases of pruritus vulvæ, thought that only 8 presented incontestable evidence of the psychogenous cause, operating alone, although in many other cases psychogenous factors were identifiable. Rogerson, in discussing this question, emphasizes that sexual factors may appear in married quite as often as single women, that they may be expressions of sexual tension, and that the eczematous manifestations accompanying the pruritus may be utilized as a method of avoiding normal relations. This is also true in the case of excoriation produced by scratching. Gillespie's case illustrates the succession of needless operative and other interventions to which the sexually grounded pruritus vulvæ may be subjected. Symptoms disappeared when this patient was released from parental domination, especially that of the mother, and her anxiety about her sexual problems was relieved. Kreis<sup>43</sup> reports 4 cases of pruritus vulvæ successfully treated by psychoanalysis.

Pruritus ani seems to be a more tempting field for psychosomatic explanations even than pruritus vulvæ. Gillespie's case illustrates the combination with exhibitionism. Gillespie points out that giving anal anesthetics to children may encourage what is almost a normal anal eroticism in the early years of life. He also points out that the most commonly produced lesion, lichenification resulting from scratching, requires not only the surgical or other treatment usually accorded it, but treatment of the sexual neurosis underlying the pruritus. Rogerson says that pruritus ani may also give a clue to the existence of unsatisfied homosexual desires, and that in these circumstances, the use of local applications is apt to be harmful rather than beneficial. Stokes,<sup>61d</sup> in a discussion of the treatment of pruritus ani, includes the anal fixation mechanism and anal eroticism among the factors in refractory cases. One of the cases he describes illustrates the concomitant occurrence of itching and lichenification of the posterior scrotal wall as an expression of sexual tension in the male. Gillespie, in his general discussion of pruritus, makes a significant correlation between the worrying depressive type of personality, which expresses uneasiness of mind by uneasiness of skin (itching) with associated scratching. He says, "The skin is chosen as a means of expressing anxiety of a general kind; although it is possible that it is so chosen because scratching acts as a temporary means of allaying the physical uneasiness produced by uneasiness of mind," just as some people take to masturbation when they are worried. This suggested relationship probably has an important bearing on the cutaneous scratch activities of the EAHF (eczema-asthma-hay fever) type of person, as brought out by Stokes.<sup>61b</sup>

**Topalgias and Phobias.** The topalgias, or localized pains in the skin and mucous membranes have been extensively discussed by Klaudre,

Gillespie, Kelman and Field. The original observations of Blocq<sup>12</sup> have been fully confirmed. Gillespie points out that the self-infliction of pain through the skin may be determined primarily through a sense of guilt. The skin may also be subjected to manipulation responsible for or secondary to skin pain, under the influence of exhibitionistic tendencies. Klauder gives 2 cases, 1 of dermatothalasia, produced by an intolerable local pruritus, and a second patient, who had insight into the psychologic mechanism of his skin symptoms and his traumatizing reactions to them which he used as a method of escape.

Klauder, in commenting on "burning tongue" which has been admirably described by Montgomery,<sup>48</sup> states that in his experience the symptom is invariably an expression of fear of cancer, often aroused by suggestions from various sources, including indiscreet remarks of physicians.

The dermatophobias include most conspicuously fear of hypertrichosis, which can develop into a severe form of obsession through a wide variety of shocks and tension-inducing circumstances. Peladophobia, fear of baldness, occurs more frequently in women than is realized. Acarophobia, or fear of parasites, can frequently run in epidemic form through a family or group of people as the result of an indiscreet remark or therapeutic overactivity on the part of a physician.

**Miscellaneous Non-classifiable Dermatoses—Psoriasis.** Bunne<sup>17</sup> who is largely responsible for the conception of "shock psoriasis," describes a case in which psoriasis apparently developed following trench experiences, disappeared following suggestion under hypnosis which did away with the effects of the trench impressions, and recurred again after suggestion under hypnosis had reestablished the original neurotic basis. Goldsmith described a case in which a profuse psoriatic eruption preceded a dreaded operation. Becker and Obermayer<sup>76</sup> confirmed for their experience the rather general impression that generalization and flare-ups of psoriasis can be brought on by tension factors similar to those underlying the neurodermatoses.

**Lichen Planus.** Goldsmith,<sup>28</sup> in reviewing the literature of lichen planus, gives as opinion rather than as demonstrated fact, the view of a number of dermatologists who feel that there is a strong psychoneurogenous background in lichen planus. To these views he does not in the main, himself, subscribe. Kartamischew,<sup>59</sup> whose exploits with hypnosis certainly need confirmatory study, caused the eruption of lichen planus to disappear in 3 out of 4 cases, by psychotherapy. Sack<sup>55</sup> secured a recovery in a woman physician by psychoanalysis. Eller<sup>23</sup> reports cases following the stock-market crash which recurred under subsequent tension disturbances. Goeckermann<sup>27</sup> reports a resistant lichen planus which presently subsided readily without further treatment when financial worries were adjusted.

**Warts.** The response of a filterable virus infection to suggestion invariably is received with surprise and incredulity by the medical mind. The original and carefully controlled work by which the psychotherapeutic factor was conclusively demonstrated was done by Bloch<sup>11</sup> at the inspiration of Heim, the geologist at the University of Zurich, who, like his father, was widely known as a wart-curer. Many interesting sidelights on Bloch's experiences are included in the discussion

by Sulzberger and Wolf<sup>62</sup> of this work. The cure of a skeptical neuro-psychiatrist is included among the cases there described. Bloch's percentage of successes was 44 for verruca vulgaris, and 88.4 for verruca plana juvenilis. Assistants of lesser prestige and convincing capacity with the method, obtained serially lower percentages (44, 35, 31, 25). One clinic patient, who could not be cured, responded promptly in Bloch's private practice. It is impossible here to give a full account of the many remarkable and interesting features of this really courageous piece of work. Studies in this country have reasonably confirmed the conclusion that at least a 50% proportion of the effect of any mode of treatment of warts may be attributable to suggestion. Allington<sup>3</sup> succeeded in showing under adequate control that colored distilled water was as effective as sulpharsphenamine when neither patient nor physician knew which was used. The contrast between Biberstein's<sup>10</sup> success with a wart "vaccine" and Cormia's<sup>19a</sup> failure by identical methods seems very probably due to suggestion; the former author having confidence in his method, and Cormia using it after deliberately depreciating the procedure as much as possible to the patient who was about to receive it.

**The General Psychotherapy of Psychoneurogenous Components in Skin Diseases.** The disposition of dermatologists to depreciate the psychogenous element in dealing with cutaneous disease has delayed materially the development of rational psychotherapy. If a clear-cut psychogenous element is recognizable, a psychiatrist may be called, but the large proportion of patients, especially those presenting the eczema-asthma-hay fever complex and the conditions influenced by the "tension frame of mind" can neither afford nor will accept extended psychiatric treatment for what they regard as the ordinary problems of human worry. Attempts have been made to place the relatively commonplace psychotherapy indicated on an accessible basis usable both by general practitioners and specialists interested in this sort of work. Useful contributions in English have been those of the Gillespie group, headed by Drake, Rogerson and Strauss at Guy's Hospital; Becker and his associates at the University of Chicago; and Stokes and his associates. Becker's various contributions recently summarized emphasize the necessity for controlling the environmental factors after an extended inquiry into the whole situation involving the family, occupation, the patient and so forth; treatment of the nervous exhaustion factor. Becker particularly emphasizes the value of reassurance, rest, including vacation, retirement and heliotherapy. Sedation with drugs occupies a varying place and is employed by Becker, usually as phenobarbital and calcium. Local treatment is regarded chiefly as palliative. Stokes and Rogerson have written in fairly close agreement on the eczema-asthma-hay fever type. In the former's account of an office technique of psychotherapy, the process of estimation of the patient's personality; landmarks in the recognition of tension; an appraisal of the vasomotor sweat and gastro-intestinal mechanisms are described. He then proceeds to the establishment of rapport, lists the commoner nervous factors; gives an office technique for catharsis and the confessional approach, and designates under eleven heads the elements or insight leads which are to be looked for in the patient's state of mind. Active treatment

begins with reassurance and readjustment, following sixteen points in a defined schedule; a technique for securing complete rest, including tension release and tension discharge; the former following closely the relaxation physiology of Jacobson.<sup>36</sup> The views and experience of Rogerson and Stokes are combined in two recent tabular summaries, the Rogerson contribution being taken from the Practitioner (1939)<sup>56b</sup> and from personal exchanges. The second summary deals specifically with the tension frame of mind which underlies such dermatoses as urticaria, rosacea and so forth.

**Basic Psychotherapy of the Eczema-Asthma-Hay Fever Patient. I. For the Infant and Prepuberal Child.** 1. Supervised play with other children under child guidance and nursery school direction.

2. Calling off of the oversolicitous and overprotective parent.

3. Treatment of the child as an equal, with explanation, patience, *laissez faire* and persuasion replacing to varying degrees parental sovereignty, severity, repression, irritability and don'ting.

4. Elimination of as many contacts as possible with the irritating ("electric") or irritable and repressive parent or other personality (school, away from home, etc.).

5. Adjustment of marital and personality conflicts between parents and insecurity-producing discriminations among children in the family as promptly and as early in life (even prenatally) as possible.

6. Discouragement of the forcing tactics, marks standards and competitive techniques of teachers, schools and sports.

7. An attempt to conserve rest—not too many visitors, not too much excitement, the midday quiet period if not nap, combating of night life, overstudy, and so on.

8. Facilities for tension discharge, non-competitive sport and exercise, *outdoor* life, nature study. The EAHF is a radically different being in the open.

9. Training in self-confidence and self-reliance—exploration, experiment, trips alone, direct relations with teachers, advisers and physicians, not mediated through the parent. Systematic but not exaggerated encouragement.

**II. For the Adult EAHF.** 1. Not too much explanation of the mechanism which characterizes or creates the mental state—at least not to the more unstable subjects.

2. An attempt in suitable cases to manage the parent problem as in the child, but more circumspectly.

3. An effort to identify in simple conversations on current activities of the patient, his plans and problems, the more obvious conflict factors, and especially the critical inferiorities, which in crisis form can precipitate asthmatic and neurodermitic explosions.

4. Education as to I-sensitiveness, kinetic drive, effect of competition, in one or two simple talks.

5. Systematic encouragement combined with emphasis on self-acceptance and de-personalization of outlook.

6. An arbitrary rest prescription with reduction in scholastic, extra-curricular, sport and social tension activities by 35 to 50% until improvement takes place. Permanent reductions in scale of attempted activity and achievement.

7. Training in a technique of relaxation.

8. Training in tension discharge via the long muscles—especially walking (cross-country preferred) from 1 to 4 hours daily, mind on the present, without thought of past or future and without time schedule or destination. This is to be supplemented by a manual hobby and an outdoor non-competitive sport (rowing, canoeing, swimming, sailing, skiing, skating, etc.). *Not* driving a car, which is a "poisonous joy" for these people.

9. Change of scene (*i. e.*, adjustment by flight) only in critical and unmanageable situations.

*Basic Psychotherapy of the Tension Personality.* 1. A talk on general principles in which the fundamental nature of tension is explained, with its relation to skin behavior.

2. The attack on the obligatory in repeated sessions by (*a*) the injunction *not to do* whatever gives the patient a feeling that it *must be done*.

3. Cutting off access of the "*must*" influences to the patient—severe cases no mail, no answering of telephone, no making or meeting of engagements, no acceptance of new, and a repudiation of up to 50% of current social commitments.

4. Provision of *physical sanctuary* (own work-room, garden, etc.) to be used for set period each day.

5. A lecture on "don't give a damn"—the "DGAD" or temporarily conscienceless attitude, illuminated by slogans of "a hundred years from now—" and so forth.

6. Drill in relaxation, both systematized as "exercises" and in waiting with patience (doctors' offices, traffic lights), substituting shrugs for jaw-clenching and nail-gnawing.

7. Provision for tension discharge by non-competitive physical, means (*notably again walking*) and manual hobbies. Stopping competitive sport and "exercise."

8. An arbitrary rest prescription based on the above elements—usually 1 hour nap or nap plus relaxation (with perhaps graded sunbathing *a la* Becker) followed if possible by 1 hour of a hobby, in sanctuary.

9. Conversational exploration of simpler conflicts (often part of a total person history) with adjustment suggestions.

10. Systematic practice at living in the moment and viewing life with serene detachment. (The "big and little Mary device" helps.)

11. Systematic encouragement, with practice in self-esteem and self-acceptance.

12. Education of the patient in the recognition of his own tension signs including watching his own voice, hand, eye, and forehead, and application of remedies.

When the assistance of the psychiatrist or an adequate psychoanalyst can be secured, results obtainable in no other way are occasionally forthcoming. On the other hand, this method has been employed too infrequently and, frankly, with too little comprehension on the part of either psychiatrist or dermatologist of the interacting mechanisms in the causal background of the psychoneurodermatoses, the allergic-infective conditions, and so forth. The psychoanalytic successes have been sufficiently referred to in the foregoing discussion. Hypnosis has

Med. Clin. North America, 15, 279, 1931; (c) J. Am. Med. Assn., 105, 1007, 1935; (d) Internat. Clin., 1 (Ser. 3), 147, 1940; Arch. Derm. and Syph., in press; (e) Arch. Derm. and Syph., 26, 478, 1932; Ibid., 29, 874, 1934; (f) J. Am. Med. Assn., 93, 438, 1929; (g) Arch. Derm. and Syph., 31, 470, 1935. (62.) Sulzberger, M. B., and Wolf, J.: Med. Rec., 140, 552, 1934. (63.) Szondi, L.: Arch. f. Derm. u. Syph., 154, 53, 1927. (64.) Vignolo-Lutati, C.: Policlinico, 25, 680, 1918. (65.) Vorhees: J. Am. Med. Assn., 48, 1837, 1907. (66.) Williams, D. H.: J. Invest. Derm., 1, 119, 1938. (67.) Wright, C. S.: Arch. Derm. and Syph., 19, 365, 1929.

**Correction:**—In Dr. Altshuler's article on "Maintenance of Nitrogen Equilibrium of Amino Acids Administered Parenterally" in the August, 1940, number, the word "nitrogen" should be omitted on page 240, line 27.

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ORIGINAL ARTICLES.

PULMONARY EMBOLISM AND HEART DISEASE.

A REVIEW OF 20 YEARS OF PERSONAL EXPERIENCE.\*

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PULMONARY embolism and infarction, recognized as a cause of dyspnea, blood spitting, and rapid death since the time of Theophilus Bonetus' more than 250 years ago, are conditions of such importance because of their frequency and clinical effect, that it is surprising that the medical profession has been so slow in paying adequate attention to them. This statement applies especially to practitioners of general medicine and of internal medicine; surgeons have long been concerned quite naturally about the complication of pulmonary embolism postoperatively, and pathologists and roentgenologists have become increasingly interested of late in the study of infarcts of the lung.<sup>2-4</sup> But so far as I know there have not yet been assembled in concise form certain medical aspects of the problem, particularly as encountered by one like myself dealing primarily with heart disease. I have been confronted time and again in the last 10 years by various angles of the association of pulmonary embolism with heart disease, including postmortem observation, not taught me in medical school or in my early hospital experience.

I have kept a file of initial diagnoses in my private patients since my start with them 20 years ago, and these I have looked over to ascertain the development of my own recognition of pulmonary embolism and infarction, first, as conditions simulating heart disease and, second, as complications of heart disease. I make no claim to more rapid progress in this respect than the next man; doubtless I have lagged behind some, but it is possible that my experience may be helpful to others. The long-time observations of a single observer are often quite useful. I am recording now only my initial diagnoses, quite a few of which have been checked by

\* Read before the Association of American Physicians, Atlantic City, May 8, 1940.



autopsy. At least as many more of the cases developed pulmonary embolism or infarction after I had first seen them, some that could be found only at autopsy. I am not including in this analysis the cases that I have seen in the open hospital wards, but those patients have demonstrated much the same points.

I shall summarize my experiences by recounting first, the increasing frequency with which I have recognized the condition; second, the possible confusion in diagnosis; third, the frequency with which pulmonary embolism complicates heart disease; and fourth, helpful signs of its presence.

We were taught in medical school to look for pulmonary embolism in cases of serious and sometimes obscure postoperative complications, but I still remember my surprise 25 years ago in the discovery postmortem in London in one of Thomas Lewis' patients with congestive heart failure of a massive hemorrhagic infarct of the lung as a cause of jaundice.

In the ten years from 1920 to 1930, I made an initial diagnosis of pulmonary embolism simulating or complicating heart disease in only 9 cases definitely and in only 7 cases questionably among 4000 patients; in 3350 patients in the last decade, on the other hand, the number of definite diagnoses has increased from 9 to 66 and of questionable diagnoses from 7 to 39. My type of practice has not changed; these cases have all been cardiac in nature or thought to have been cardiac when referred to me.

Of the total 75 definite cases, only 29 were diagnosed in the first 16 of the 20 years among 6000 patients, while the balance of 46 cases were noted among 1350 in the last 4 years. I am sure, in retrospect, from my case records and from review of the autopsy reports at the Massachusetts General Hospital that there has not been such an amazing increase in pulmonary embolism and infarction rather suddenly in the last 5 to 10 years, as these figures would suggest, but that a large part at least of the increase has been due to our better recognition of the condition, especially in the clinic, and also even in the autopsy room, though to a lesser degree. I find that I diagnosed pneumonia, bronchial or atypical lobar, and also sometimes congestive failure between 1920 and 1930 in patients who today would be quite clearly recognized as having pulmonary infarction. Even the pathologists believe that they on occasion were calling some infarcts pneumonia, as were the roentgenologists. In our clinic at the moment, on the other hand, there is, in our enthusiasm, probably more danger of overdiagnosis of pulmonary embolism than of its underdiagnosis.

Of the total 75 definite cases referred to above, 28 simulated and 47 complicated heart disease. The acute cor pulmonale was first diagnosed in October, 1932,<sup>7-9</sup> and I have since seen 13 other private patients who I thought deserved this designation. Of the 75 definite cases, 42 were males and 33 were females. The age

range was from 15 to 87, with the majority in the 50's and 60's. The cardiac diagnoses in those cases with definite heart disease in which pulmonary embolism or infarction occurred as a complication were coronary disease, mostly with myocardial infarction and with or without hypertension, in 26, rheumatic heart disease, mostly with mitral stenosis and auricular fibrillation in 15, hypertensive heart disease in 2, patent ductus arteriosus with subacute bacterial endocarditis in 1, and cardiac enlargement with no other evident abnormality than chronic auricular fibrillation or flutter in 3 cases (2 of fibrillation and 1 of flutter). Of the 47 cases, 29 were in congestive failure and 15 showed auricular fibrillation. Peripheral phlebitis was evident in only a few cases, but it is probable that the majority might have shown such a lesion if we could have explored the veins; at least, that is the lesson to be derived from the postmortem findings at the Massachusetts General Hospital where some 70% of the medical pulmonary embolism cases have phlebitis that gives little or no clinical evidence of its presence. However, the frequency with which large hearts in failure with auricular fibrillation were present in my group allows either the heart itself or the veins or both to be incriminated as the source of the emboli to the lungs; the great preponderance of pulmonary emboli probably comes from the leg and pelvic veins. Rare cases of pulmonary infarction may have originated from pulmonary thrombosis *in situ*; it is also probable that a small embolus may be backed up by thrombosis after it has blocked a vessel.

There are four remaining points which I would like to emphasize. The first is the frequency with which pulmonary embolism and infarction may occur in medical as well as in surgical cases: in a series of 370 cases of pulmonary embolism and infarction analyzed at autopsy at the Massachusetts General Hospital by Hampton and Castleman,<sup>3</sup> 40% were postoperative with 58% infarcts, 30% were cardiac with 90% infarcts, and 30% were non-cardiac medical with 62% infarcts. The second point is that some of the medical cases without chronic heart disease simulate cases of heart disease itself by the development of pulmonary artery and right ventricular dilatation, sometimes with engorgement of the neck veins and a characteristic electrocardiogram. This combination of findings we have labelled the acute cor pulmonale,<sup>7-9</sup> but it is, of course, present in only a small minority of cases of pulmonary embolism, for there must be a large enough obstruction to the pulmonary circulation to overload the heart in the first place but not large enough to cause early death in a state of shock. The chief importance in the recognition of the acute cor pulmonale is to differentiate it from acute coronary thrombosis with myocardial infarction. The transition of acute cor pulmonale to a chronic cor pulmonale is quite possible,<sup>2</sup> but we have not yet studied it ourselves. One other way in which pulmonary infarction can simulate heart disease or rather heart

failure is to produce signs, especially dullness and râles at one or both lung bases, which are taken for pulmonary edema with or without a little hydrothorax, in a patient who already has heart disease but is not actually in failure.\*

The third point concerns the ease and frequency with which pulmonary embolism and infarction complicating heart disease can be overlooked, especially if there is already congestive heart failure behind which, at the lung bases for example, the infarcts may hide.<sup>6</sup> Clues may be found, such as the periodic occurrence of unexplained attacks of faintness, prostration, dyspnea, or *tachycardia* (especially), followed by fever<sup>5</sup> and leukocytosis, or by an increase of fever, if such is already present due to a hidden phlebitis or perhaps in slight to moderate degree from the congestive failure itself; discomfort on breathing and an obscure slight jaundice may also be clues. There may or may not be any chest pain, or cough, or blood spitting. Emboli are usually multiple and recurrent and hence punctuate the chart rather characteristically to explain what used to be called bronchopneumonia, although it is true that pneumonia may complicate pulmonary infarction and be found with it at autopsy. It is of interest that of 50 cardiac patients with congestive failure examined postmortem, reported recently by Dr. Kinsey and myself,<sup>5</sup> every single one showed some complication which may well have been the proverbial last straw; pulmonary infarction headed the list with 24 cases, bronchopneumonia was next with 20, and acute rheumatic infection and acute coronary thrombosis tied for third with 8 each; there were multiple complications in several cases.

Finally, the fourth point is this: in a cardiac patient with congestive failure who fails to respond as he should to treatment, it is important to bear in mind the possibility not only of pulmonary infection or rheumatic fever, but also of the more common complication, namely, pulmonary infarction.

**Summary.** 1. Pulmonary embolism has surprisingly failed to attract the interest and attention it has deserved from general practitioners and those working primarily in the field of internal medicine, in contrast to its long-standing recognition by surgeons and obstetricians as a serious complication after operation, accident, or childbirth. It needs emphasis as a medical disease because of its frequency and importance in non-surgical and non-obstetrical cases.

2. My own experience is probably typical of that of many who have only in recent years begun to be on the lookout for pulmonary

\* It is of additional interest and importance that pulmonary embolism alone may on occasion precipitate pulmonary edema or asthmatic breathing, and so may simulate acute left ventricular failure; especially does this happen if mitral stenosis or some strain involving the left ventricle (hypertension, aortic valve disease, or myocardial infarction) is already present. It is quite possible that sometimes in the presence of limited myocardial reserve there may be a two-fold reason for pulmonary edema or asthmatic breathing, namely the pulmonary embolism itself and left ventricular failure. .

embolism. In 10 years from 1920 to 1930 I made an initial diagnosis of this condition either simulating or complicating heart disease in only 9 cases definitely and in only 7 cases questionably among 4000 patients; while in the last decade among somewhat fewer patients (3350) there were nearly 7 times as many such cases diagnosed (66 definite and 39 questionable).

3. About one-third of my cases simulated and the remainder complicated heart disease. Of the former (28 in number) one-half (14) showed the signs of the acute cor pulmonale described by McGinn and myself in 1935, including characteristic electrocardiographic abnormalities. In most cases pulmonary embolism is either so mild or so rapidly fatal that such signs are not present or the patients are examined only after the height of the effect of the pulmonary arterial obstruction has passed.

4. Pulmonary embolism and infarction are easily overlooked, especially in the presence of congestive heart failure, when they are most common; or they are erroneously diagnosed as something else, especially pneumonia, congestive heart failure, or coronary thrombosis.

5. Clues to the diagnosis lie in the occurrence of unexplained fever, leukocytosis, tachycardia, faintness, prostration, dyspnea, or even jaundice (from hemolysis of the infarct plus an engorged liver) especially in a cardiac patient with heart disease (and particularly in the presence of mitral stenosis or heart failure).

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## COBRA VENOM.

### ITS USE IN STENOCARDIA.

#### PRELIMINARY REPORT.\*

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THE tremendous strides made in the diagnosis of coronary disease both clinically and graphically have become part of the accumulated

\* We are indebted to Hynson Westcott & Dunning, Inc., of Baltimore, for their generosity in furnishing all the material for this study.

history of medical progress. However, the treatment of the condition has not kept step and has lagged far behind, as we all sadly realize. For the acute attack of coronary thrombosis our entire armamentarium may almost be summarized by one word—morphine. Be this as it may, the clear-thinking physician soon realizes that, though the double-edged sword of the opiates may be used in the original attack, the danger of habituation is too great to allow him to use the drug at frequent intervals for stenocardia of the lesser degree from which patients frequently suffer. This type of stenocardia is seen very often during the first 2 weeks following the onset of the thrombosis even while the patient is resting quietly in bed, and is also seen lasting for short periods at times, even months or years after the initial attack. Though many drugs have been suggested and used for the relief of this most trying pain, none has been very successful until the advent of cobra venom which, if it fulfills its original promise, will place us one step higher in our climb to successful treatment of those unfortunates who have stenocardia while at rest.

Though some venoms have been used in medicine for various purposes, there is one group, that of the cobra, which exerts an influence in a very important direction, namely, on pain. It is gratifying to note that it was an American physician, Adolph Monaelesser, who became interested most particularly in these venoms. At the Pasteur Institute he, Calmette, Olivera, and Dumatras prepared the groundwork for the use of cobra venom in the relief of intractable pain of various causes.<sup>6a</sup> Dr. David Macht, who has had much experience with cobra venom and has been instrumental in developing its pharmacology in the treatment of painful conditions,<sup>6b,c</sup> suggested its use in the relief of those suffering from repeated attacks of stenocardia while at rest. He had made careful studies of the physiologic, pharmacologic, and psychologic effects of this venom and found that the drug could be prepared in a stable form and biologically assayed.<sup>6d</sup> Furthermore, the drug acted upon the higher nerve centers to produce its analgesia, being in this respect similar to morphine, differing from it, however, in that it was not habit-forming nor did it produce the mental depression of the opiate. In fact, mental efficiency seemed to be somewhat stimulated by cobra venom.<sup>6e,8a</sup> As part of this same mental stimulating factor, it is worthy of note that, whereas morphine and the other opiates contract or narrow the fields of vision, cobra venom widens them.<sup>8b</sup> The drug also differs from morphine in several other ways. In the first place, morphine acts very quickly after its administration; cobra venom, on the other hand, may take many hours or even a day before its action will be manifest. Further, morphine loses its effect within a few hours, whereas cobra venom has a rather marked cumulative effect which can be put to excellent advantage in treatment.<sup>6d</sup> In one respect, aside from its analgesic

action, cobra venom is similar to morphine; they both depress the respiratory center. Though in the therapeutic doses used there is very little danger of harmful depression of this vital center, nevertheless it is a point that must be kept in mind whenever the drug is employed.<sup>6c</sup> In order to reassure the physician as to the leeway between the usual therapeutic dose and one which may depress the vital respiratory center, several personal communications from Dr. Macht are illuminating. Five mouse units is considered to be the usual human starting dose; however, a number of physicians have administered 10 mouse units of the venom daily for from 1 to 3 weeks without in any way depressing the respiratory center. A few have even given 15 mouse units daily for several days. One physician reports the administration of 25 mouse units of cobra venom daily to a patient having most severe pain from generalized bone metastases from a breast cancer and states that he observed no ill-effect. In other words, cobra venom has been given in doses from two to five times that which is considered a safe starting dose with absolutely no evident depression of the vital respiratory center. The therapeutic dosage of the cobra venom is comparatively so small and the margin of safety so wide that there is little danger of medullary paralysis. So far, in fact, in spite of increasing use and dosage of the venom, no reports of respiratory embarrassment have been received. The only other reactions worth mentioning are purely local ones at the site of injection and are probably due to the tri-cresol added to the solution.<sup>6c</sup> Before leaving this phase of the discussion, it is pertinent to add that in experimental work conducted on rabbits, tremendous doses of venom failed to demonstrate any untoward effects upon kidney or liver function.<sup>7</sup> Though cobra venom is rather poor in cytotoxic elements compared to other venoms, it is exceedingly important to rule out any danger from this source. Huge doses of cobra venom injected into rabbits both intramuscularly and intravenously produced no significant changes in the blood cytologic or chemical picture.<sup>9</sup> In addition to these painstaking studies of Macht, articles by other investigators have appeared both here and abroad, all referring to the use of the venom for a variety of painful conditions and stressing the apparent lack of harmful side effects.<sup>2-5,10-14</sup>

Supported by this weight of evidence and by the fact that Bullrich,<sup>1</sup> in South America, had used the drug in certain types of angina pectoris, we felt justified in attempting to give our treatment-resistant patients this non-habit forming drug, apparently capable of relieving their repeated attacks of stenocardia.

At this time we have used the drug in but a small group of 5 cases with stenocardia at rest. These patients are not too common but present a problem which taxes and baffles the physician who finds himself between the Scylla of morphine addiction and the Charybdis of exhausting pain. We wish to report this group because cobra

venom was the only drug which gave them freedom from pain after all the other therapeutic agents except morphine failed. The nitrites, xanthine derivatives, papaverine, and other supposed coronary dilators were used in almost every case with very little or indifferent effects. Therefore, we feel that if we could get beneficial results in this group, the promise of the drug is too great to withhold until more numerous and detailed clinical studies can be performed.

Our patients were given 5 mouse units intramuscularly as the initial dose. This was repeated on the following 2 or 3 days. Then 1 ampule was given every other day for 5 or 6 doses. Finally, the dosage was reduced to 5 mouse units once or twice weekly. It is pertinent to note that Steinbrocker<sup>13</sup> has given as much as 10 and 15 mouse units in many of his cases without ill-effects. In other words, as with any drug, the dose must be increased until the desired therapeutic effect is achieved without producing toxic symptoms.

The cases selected by us represent stenocardia in its varied aspects.

**Case Abstracts.** CASE 1.—A white woman, aged 69, complained of attacks of precordial pain radiating to the left shoulder and accompanied by a sense of constriction in the throat. The cardiac examination was negative except for a blood pressure of 180 systolic, 90 diastolic, a pulse rate of 108 per minute, and an electrocardiogram which showed evidences of myodegeneration. On August 6, 1939, she was given 2.5 mouse units of cobra venom, followed by 5 mouse units on the 2 following days and then 5 units every other day for 3 weeks. After 2 days of treatment, her attacks were reduced to 1 a day from a level of 10 to 12. At the end of 2 weeks all attacks disappeared, and the cobra venom was stopped 1 week later. On her last visit her blood pressure was essentially the same and her electrocardiogram showed no regressive changes.

CASE 2.—A white laborer, aged 54, had had attacks of substernal pressure for some months before he was first seen on October 22, 1938. By that date these attacks were coming on even at rest, each lasting 10 to 30 minutes. This patient had a blood pressure of 225 systolic, 125 diastolic, tortuous fundal vessels, cardiac enlargement to the left and a soft blowing systolic mitral murmur. The electrocardiogram showed the usual changes seen in hypertension. During the next year he had at least one or two attacks of substernal pressure daily while at rest as well as whenever he walked. On October 12, 1939, he received 5 mouse units of cobra venom and this dose was repeated on 5 successive days. At this point he was free of pain for the first time in over a year. The dose was then reduced to 1 ampule every other day for 2 weeks and then to 2 ampules weekly. At the end of 4 weeks, the dose was reduced to 1 ampule weekly. This was enough to keep him free of pain while at rest, but he still had an occasional seizure while walking. When last seen in March, 1940, the patient showed no electrocardiographic or physical damage as a result of the cobra venom.

CASE 3.—A white woman, aged 60, had had a coronary occlusion 3 months before her first visit on February 10, 1940. She was then suffering from attacks of severe substernal pressure radiating into the left arm, severe enough to awaken her from sleep. She had a blood pressure of 220 systolic, 110 diastolic, a systolic blow over the mitral area and an electrocardiogram which showed a left bundle-branch block. There was no cardiac enlargement. Since she was seen in consultation, she was treated by her family physician who gave her 5 mouse units on 3 successive days and then 1 am-

pule every other day for 2 weeks followed by 2 ampules weekly thereafter. A letter from him states that she had had marked relief since the use of the cobra venom though she still gets an occasional attack. Here too, there has been no cardiac damage, as shown by the electrocardiogram, from the use of cobra venom.

CASE 4.—A white male, aged 51, was first seen in consultation in 1934. He was then complaining of pain in the precordium which usually came on during effort, but was occasionally also present at rest. Physical examination was negative at that time except for some cardiac enlargement to the left and a blood pressure of 115 systolic, 70 diastolic. A diagnosis of angina pectoris was made. In these 6 years the patient has had many periods during which his pain was so severe for several days at a time that only morphine gave him relief. He started another such bout on October 20, 1939. Five mouse units of cobra venom were given him daily for 3 days before he experienced any relief. An ampule was given him twice daily thereafter until November 30, when treatment was stopped. The patient was free from pain during this entire period for the first time since 1934. He returned again on January 3, 1940, complaining of having had pain during the last 2 weeks of December. He was given two injections of cobra venom with such singular relief that he did not return until March 9. Once more he received the venom, every other day for three doses and then twice weekly for about 1 month, again with complete relief of pain.

CASE 5. A white male, aged 61, had had coronary occlusions in 1934 and in 1938. On January 24, 1940, he developed acute cardiac failure, which was controlled readily with morphine and aminophyllin intravenously. On January 26, however, he suffered another coronary occlusion. After this, he began to have one or two attacks of such severe substernal pressure nightly that morphine was necessary for relief. Finally, after all other remedies but morphine were found inadequate, cobra venom was started on February 22, 1940. He received 1 ampule daily for three doses and then every other day for 3 weeks. Thereafter, he received 1 ampule weekly with adequate control of his pain. It was only after the cobra venom began to give him relief from pain, that the patient showed clinical improvement. Blood counts and electrocardiograms failed to show any damage from the cobra venom.

We wish to emphasize that, though 5 cases are very few, they were all patients who were either very ill or upon whom every other type of medication had been used to little or no avail. Therefore, if cobra venom could work here, it could be expected to work successfully in a large percentage of similar cases. This work is being carried further as cases become available.

Let us reemphasize the fact that cobra venom cannot be used to relieve the pain of an acute attack of coronary thrombosis, since its action is slow and cannot be expected to reach its full effect a few hours after an injection. In fact, it may sometime take 24 to 48 hours for the drug to become effective at all. The user must never expect his patient to be relieved of symptoms until at least 2 or 3 injections have been given. It can be readily seen, therefore, that by no stretch of the imagination can this be considered an emergency measure.

Though Macht<sup>6b</sup> has reported some unfavorable reactions from the drug, as has Steinbrocker,<sup>13</sup> in our group we have noted none. The only complaints were those that follow any intramuscular



injection. Several of the patients, when they discovered the nature of the drug they were receiving, had slight psychologic misgivings which were soon corrected by reassurance.

**Summary.** We have used a new drug, cobra venom, in certain cases of stenocardia which were helped by no other medication but morphine. All 5 cases were relieved of their symptoms when adequate doses of the drug had been given. No untoward reactions were observed. We are convinced that a valuable therapeutic agent has been added to the armamentarium of the cardiologist for the relief of stenocardia.

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### HEREDITY IN PERNICIOUS ANEMIA.

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THE importance of heredity as a factor in the pathogenesis of disease has long been recognized. Evidence is accumulating that the hereditary occurrence of pernicious anemia is more than merely a coincidental curiosity.

In 1891, Klein<sup>12</sup> reported the presence of Addisonian anemia in 4 members of one family, a sister and 3 brothers. In 1899, Bramwell<sup>2</sup> mentioned the occurrence of the disease in a patient and his brother, mother, 2 uncles and an aunt. Caccini,<sup>4</sup> in 1900, reported the presence of this disease in a father, son and daughter. In 1908, after a review of 1200 cases, Cabot<sup>3</sup> concluded that the "disease did not appear to be hereditary." In 1907, Gulland<sup>8</sup> called attention to 3 patients whose father had died of pernicious anemia. In 1911, Patek<sup>18</sup> referred to the presence of pernicious anemia in 2 brothers, a sister, paternal aunt and cousin. In 1913 Bartlett<sup>1</sup> reported its occurrence in a father and 3 sons. Gulland and Goodall,<sup>9</sup> with a personal experience of approximately 500 cases, reported that pernicious anemia not uncommonly occurs in more than one member of the same family.

It is noteworthy that this apparently hereditary incidence in pernicious anemia was merely mentioned as an incidental and curious phenomenon.

In 1920 Minot<sup>16</sup> did not consider the occurrence of pernicious anemia in members of the same family as common, and regarded the hereditary factor as unimportant.

As early as 1918 Schauman<sup>19</sup> regarded the hereditary incidence of pernicious anemia as a frequent and important factor. In 1921 Levine and Ladd<sup>13</sup> discovered a distinct familial incidence in pernicious anemia while studying 143 cases. Nine patients were stated as having a "definite family history" of the disease in some other member of the family. In 1927 Minot<sup>15</sup> stated that while pernicious anemia "may occur in the same family, this is unusual." But in 1936 Castle and Minot<sup>5</sup> noted that "when complete histories are available, at least 18 per cent of the patients will be found to have one or more close relatives who have the disease." Meulengracht<sup>14</sup> believes that heredity plays an important rôle in the disease, but feels that more work is necessary before this point can be proved.

There is an increasing tendency in more recent literature to regard the hereditary incidence in pernicious anemia as an important factor in the pathogenesis of the disease. Publications by Gilford,<sup>7</sup> Meulengracht,<sup>14</sup> Hurst,<sup>10</sup> Dorst<sup>6</sup> and Schemm<sup>20</sup> tend to support this view. Mustelin<sup>17</sup> has advanced the hypothesis that pernicious anemia is a dominant property, depending on a single gene. Kaufmann and Thiessen,<sup>11</sup> in a study of the subject, conclude that the disease is transmitted as a dominant characteristic; they believe there are members of families who do not have pernicious anemia but are "carriers" of the disease from the hereditary standpoint.

In any study of the hereditary incidence in pernicious anemia there are a number of inherent difficulties which confront the observer. Among these may be mentioned: 1, errors in diagnosis; 2, difficulty in pursuing thorough investigation due to scattering of families; 3, failure to recognize pernicious anemia as a cause of death in some families; 4, deaths from accidents or disease early in the life of members of a family may affect the statistics; 5, being a disease that occurs in the later decades of life, members of a family not having the disease may eventually show evidence of it.

In an analysis of 645 unselected, authenticated cases of pernicious anemia at this Institute, 51 case histories revealed the presence of the disease in one or more other members of the same family. This gives an incidence of 7.9%. In 8 of these 51 family histories, the diagnosis of pernicious anemia in other members of the family was also made at this Institute; in 8 the diagnosis was made by the family physician. In the remaining 35 cases, the patient's report of the disease in his family was the sole method available for establishing a positive family history. It is obvious, therefore, that the true incidence in this series of 645 cases is probably less than 7.9%, inasmuch as some of the cases diagnosed as pernicious anemia and

reported only through the patient may have had some other type of anemia.

TABLE 1.—THE OCCURRENCE OF PERNICIOUS ANEMIA IN 51 FAMILY HISTORIES.

Other members of family having pernicious anemia.	No. of families.	Total No. of individuals having pernicious anemia in 51 families.	Members of family known to have died of pernicious anemia.
Mother	10	20	8 of 10 mothers
Father	8	16	6 of 8 fathers
Sister	11	22	3 of 11 sisters
Brother	5	10	3 of 5 brothers
Case of twins; no other family member has pernicious anemia	1	2	None
Two brothers	2	6	2 brothers 1 brother
Brother, sister	3	9	None Brother and sister None
Uncle	1	2	None
Father, brother	1	3	Father, brother
Paternal aunt	1	2	None
Paternal grandfather Brother	1	3	Paternal grandfather Brother
First cousin	1	2	None
Mother, uncle, maternal aunt, sister	1	5	Mother, uncle, maternal aunt
Father, paternal uncle, one of twin sisters	1	4	Father
Mother, 2 maternal aunts	1	4	Mother, 2 maternal aunts
Two brothers, 1 sister	1	4	Two brothers
Mother, sister	1	3	Mother, sister
Mother, uncle, maternal aunt, sister	1	5	Mother, uncle, maternal aunt
Father, paternal uncle, one of twin sisters	1	4	Father
Mother, 2 maternal aunts	1	4	Mother, 2 maternal aunts
Two brothers, 1 sister	1	4	Two brothers
Mother, sister	1	3	Mother, sister
Mother, maternal grandmother, maternal aunt	1	4	Mother, maternal grandmother, maternal aunt

Of these 51 families the only other member, besides the patient, found to be affected was the mother in 10 instances, the father in 8, the sister in 11, and the brother in 5. Two family histories revealed the presence of pernicious anemia in an uncle and paternal aunt respectively.

Five families are represented in this series in which 3 or more of the immediate children had the disease. In one family the mother, uncle, and maternal aunt died of pernicious anemia, and the patient and her sister were diagnosed here as having the disease. In another family the paternal uncle died of pernicious anemia, the father, and one of twin sisters, and the patient were diagnosed here as having this disease. A mother and 2 maternal aunts of a patient died of pernicious anemia in another family. One case history revealed the death of a mother, maternal grandmother and maternal aunt.

Two families were particularly interesting. In one of these, twin sisters, age 35, the only siblings, were here diagnosed as having pernicious anemia. In the other, a family of 4 children, 2 brothers died of the disease and 2 sisters were here diagnosed as having pernicious anemia. The father of this family died "cause unknown" and the mother died of "dropsy." One of these sisters had 8 children who were said to be in good health, ages not given.

In a study of 377 patients with pernicious anemia at this Institute, Dr. Lloyd R. Gates asked the patients "Did any of your relatives have pernicious anemia?" Of these, 27.3% answered "Yes," and 72.1% answered "No." In 536 patients of a similar age and location group, but who did not have pernicious anemia, the answers to the same question were "Yes" 9.1% and "No" 90.9%. These data, of course, do not indicate that the relatives actually had Addisonian pernicious anemia, but they are suggestive, inasmuch as the same type of error (false diagnosis) could be present in the control series as well as the pernicious anemia group. In both of these groups, however, the observed difference was 2.5 times its standard error.

The hereditary incidence in this series of cases is 7.9%. It does not approach the 18% figure given by Minot and Castle. Although the former percentage is minimal, this study only includes a limited range of relatives. As Meulengracht has pointed out, pernicious anemia is relatively uncommon, and in his investigation of the family histories of a number of control individuals he gives the incidence as zero. The percentage of 7.9% is, therefore, too high to be due to mere chance. It is believed, however, that a similar series of cases more closely controlled would likely reveal a higher incidence. Furthermore, the repeated occurrence of the disease in several members of the same family does not appear to be due to chance alone.

Another view of the problem, using these data, is that 92.1% of

the patients with pernicious anemia knew of no hereditary involvement. In other words, a patient may be advised that there is over 92% chance that his children will not have pernicious anemia; and that there is the same chance that if his parents had pernicious anemia, he would not have it. The question as to whether multiple cases in one family are fortuitous or the result of a hereditary tendency to the disease, or to a common abnormality in the environment, is still not clear. The peculiar anthropomorphic characteristics which patients with pernicious anemia have would make it seem that at least some of the "soil" of the disease is familial.

**Summary.** In a series of 645 cases of pernicious anemia the percentage of familial incidence is 7.9%. In this series 5 families are represented in which 3 or more of the immediate children had the disease. Five additional families reveal the presence of pernicious anemia in 3 or more members of the same family in successive generations among the lineal or collateral descendants. An authenticated instance of the disease occurring in twin sisters is reported.

It is suggested by this study that a definite familial hereditary factor exists in pernicious anemia. Continued interest and investigation of this question are advisable because of its obvious practical significance.

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## THE EFFECT OF NICOTINIC ACID ON BLOOD COAGULATION.

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IN a previous paper,<sup>1</sup> it was reported that the blood of patients suffering from chronic brucellosis often clots slowly, retraction of the coagulum is imperfect, and the yield of serum is low. Adminis-

tration of nicotinic acid to such patients was followed by complete correction of these defects.

The addition of nicotinic acid *in vitro* to samples of whole blood from 6 brucellosis patients showing this abnormality (0.6 mg. per cc. blood) reduced the clotting time from an average of 11.3 to 6 minutes and clot retraction, imperfect or absent in the controls, was complete within 3 hours in all instances. Likewise, the clotting time of plasma from 25 brucellosis subjects was reduced an average of 36% by the addition of similar concentrations of nicotinic acid *in vitro*.

When a solution of nicotinic acid (0.6%) was applied by cotton pledget to tooth sockets following extraction, a firm, permanent clot resulted in from 1 to 2 minutes; untreated control sockets on the same patient followed the usual course, often bleeding for several hours. Similarly, local application to small cuts caused an immediate stay of blood flow.

The internal use of nicotinic acid in 2 cases of typhoid fever was followed by striking disappearance of delirium, coma, and intestinal bleeding. In 1 of these cases, due to a mistake in orders, nicotinic acid was discontinued after 10 days, during which time the patient seemed to be convalescing perfectly; within 24 hours delirium recurred, and intestinal hemorrhage with death ensued.

In another patient, who had suffered for years from profuse and prolonged nosebleeds, it was found that, except for a barely detectable coagulum at 20 minutes, the blood was still fluid at 24 hours. Oral administration of 100 mg. nicotinic acid 3 times daily was followed by a clotting time of 6 minutes; and in the 4 months during which this treatment was continued, there was no recurrence of bleeding.

One patient, diagnosed as having hypoplastic anemia, had a bleeding time of 15 minutes without prolongation of clotting time (2 minutes). After oral administration of nicotinic acid for 1 week (100 mg. 3 times daily) the bleeding time was 8 minutes.

A 13-year-old male patient, ill for 9 months with low-grade fever of unknown etiology, exhibited marked tendency to bleed. The platelet count had varied from 25,000 to 50,000 during this illness. He bled so profusely from a small puncture wound made in the ear for test purposes that more than 100 sheets of filter paper were soaked with blood in the 35 minutes before bleeding was stopped mechanically. After oral administration of 100 mg. nicotinic acid 3 times daily for 1 week, the bleeding time was reduced to 15 minutes and only 3 sheets of filter paper were required to absorb the blood lost in the test.

The addition of nicotinic acid to blood samples from 3 patients with acute catarrhal jaundice (0.12 to 0.6 mg. per cc. of blood) reduced the clotting time from an average of 14 to 6 minutes. On

blood from a patient with hemophilia nicotinic acid had no effect when added *in vitro*.

*Experimental Observations.* In an effort to elucidate the mechanism responsible for the above results, experiments were performed to determine whether nicotinic acid can be substituted for any of the factors involved in normal coagulation. According to Eagle,<sup>2a</sup> calcium and platelets (or other tissue extracts) appear to constitute a proteolytic enzyme which converts prothrombin to thrombin, and the latter then causes the transformation of fibrinogen to fibrin. By preparing these various reagents in purified form, it was possible to compare their action, separately and in different combinations, with that of nicotinic acid. The following experiments indicate that the action of nicotinic acid does not duplicate that of any of these factors.

Thromboplastin was prepared by Quick's<sup>4b</sup> method; prothrombin by Mellanby's technique (Eagle<sup>2b</sup>) or Eagle's method (Tillett<sup>5</sup>); and purified fibrinogen by Eagle's<sup>2c</sup> procedure.

In this series of experiments, it was found that oxalated plasma could not be made to clot by the addition of any concentration of nicotinic acid (0.1% to 0.6% in the final mixture); hence nicotinic acid is not equivalent to calcium. Likewise, plasma from which the platelets were removed by filtration could not be clotted with similar concentrations of nicotinic acid; it is evident, therefore, that the action of nicotinic acid does not duplicate that of platelets.

Nicotinic acid is also not the equivalent of the thromboplastic principle found in tissue extracts. The addition of thromboplastin to 6 samples of plasma caused clotting in 19 seconds; while, when nicotinic acid (1.2 mg. to 1 cc. plasma) or physiologic saline was used, the clotting time averaged 139 seconds.

Nicotinic acid does not convert prothrombin to thrombin. Buffered (pH 6.8) prothrombin, subjected for 15 minutes to the action of nicotinic acid and then added to purified fibrinogen, failed to induce clotting, even after the addition of calcium.

Nicotinic acid does not increase the yield of thrombin from prothrombin: 0.6 mg. of nicotinic acid and 0.1 cc. of 2.5% calcium chloride were added to 1 cc. of prothrombin solution.<sup>5</sup> The resulting solution was diluted and added to 0.2 cc. plasma in amounts varying from 0.1 to 0.005 cc., at which point the material was inactive. At each dilution, the behavior of the thrombin obtained from the specimen containing nicotinic acid was identical with that obtained from the saline extractive.

Finally, nicotinic acid does not duplicate the action of thrombin itself, for purified fibrinogen buffered at pH 6.8 was not clotted by the addition of nicotinic acid (0.1% to 0.6% in the final mixture).

*Apparent Neutralization of Antithrombin by Nicotinic Acid.* Since it is known that antithrombin inhibits blood clotting, experiments were devised to determine whether nicotinic acid would induce

the coagulation of blood in which the antithrombin content was increased. This abnormality was produced by adding heparin (Hynson, Westcott and Dunning; 0.2 mg. per cc. of blood) to human blood, and also by shocking dogs by anaphylaxis<sup>3</sup> or peptone.<sup>4a</sup> Under these conditions, it is well established that the failure of the blood to clot is due to its increased content of antithrombin; and if nicotinic acid could induce coagulation of such blood, it would be reasonable to assume that neutralization of antithrombin had occurred.

Non-coagulable blood from 2 dogs in anaphylactic shock clotted in 4 minutes after the addition of 2.5 mg. nicotinic acid per cc. of blood.

Nicotinic acid failed to shorten the coagulation time significantly in 9 of 31 samples of blood from dogs in peptone shock. In the remaining 22 instances, however, samples containing nicotinic acid clotted in an average of 17 minutes, whereas none of the controls clotted in less than 12 hours and many remained fluid after 24 hours (Table 1). The concentrations of nicotinic acid required to produce this effect varied in different samples, probably due to the varying amounts of antithrombin present; in most instances, 3.3 mg. of nicotinic acid per cc. of blood was used.

TABLE 1.—EFFECT OF NICOTINIC ACID *in Vitro* ON BLOOD OF DOGS IN PEPTONE SHOCK.

Clotting time in minutes.		Concentration N. A. in mg. per cc. of blood.
Without N. A.	With N. A.	
∞	C 1.5	0.5
P 200	C 12	6.0
∞	C 6	6.0
P 720	C 6	3.3
∞	C 8	3.3
P 720	C 10	3.3
P 265	C 6.5	3.3
P 720	C 17	3.3
P 720	C 20	3.3
P 316	C 8	3.3
Sl 720	C 60	3.3
P 720	C 7	3.3
C 720	C 8	2.5
C 720	C 7	2.5
P 720	C 11	3.3
∞	C 35	1.5
Sl 720	C 5	1.5
∞	C 67	2.0
∞	C 9	1.5
∞	C 13	2.0
∞	C 13	1.5
∞	C 36	2.0

Abbreviations (in all tables): N. A. = Nicotinic acid; Sl = slight trace of coagulum; P = partial clot, not holding on inverting tube; C = complete, firm clot.

In 5 samples of heparinized human blood the coagulation time was reduced by nicotinic acid (6 mg. per cc. of blood) from partial clotting at 40 minutes (average) to complete clotting at 10 minutes (average) (Table 2).



TABLE 2.—COMPARISON OF COAGULANT ACTION OF NICOTINIC ACID WITH THAT OF OTHER ACIDS. HEPARINIZED BLOOD.

Acid.	Heparin (mg.).	Saline (cc.).	Results.				
			Subject A.	Subject B.	Subject C.	Subject D.	Subject E.
0 (normal control) . . .	0	1.0	P 4 C 7	P 5 C 7	C 8	P 9 C 12	P 5 C 8
0 (heparin control) . . .	0.2	0.9	Sl 33 P 37	P 38	P 60	P 32	P 33
Nicotinic 9 mg. (0.9 cc. 1%) . . . . .	0.2	0	C 11	C 8	P 8 C 10	P 9 C 12	P 8 C 10
Acetic . . . . .	0.2	0	P 18	P 22	P 23	P 35	P 25
Citric . . . . .	0.2	0	P 22	P 25	P 30	Sl 27 P 31	P 25
Lactic . . . . .	0.2	0	P 17 C 26	P 15	P 35	Sl 27 P 39	P 21
Oxalic . . . . .	0.2	0	P 26	P 18	P 31	P 27	P 21
Hydrochloric . . . . .	0.2	0	P 32	P 34 C 38	P 60	Sl 36 P 50	P 37 C 46
Nitric . . . . .	0.2	0	P 23	P 31	P 31 C 40	P 23	P 21
Sulphuric . . . . .	0.2	0	P 23	P 23	P 24	P 28	P 17 C 21

1.5 cc. whole blood in each tube. Volume and pH of other acids duplicated those of nicotinic acid.

TABLE 3.—COMPARISON OF COAGULANT EFFECT OF NICOTINIC ACID WITH THAT OF OTHER ACIDS (BLOOD FROM DOGS IN PEPTONE SHOCK; *in Vitro*).

Dog No.	Clotting time (saline control).		Clotting time after addition of various acids.							
	Before shock.	After shock.	Nico-tinic.	Acetic.	Citric.	Lactic.	Oxalic.	Hydro-chloric.	Nitric.	Sul-phuric.
1	8	P 265	C 6.5	P 12	P 103	P 170	P 720	P 265	P 11	P 265
2	6	P 720	C 17	P 65	P 720	Sl 720	Sl 720	Sl 720	P 380	Sl 720
3	8	∞	∞	P 360	∞	∞	∞	∞	Sl 720	∞
4	6	Sl 720	C 720	P 720	P 720	∞	Sl 720	∞	Sl 405	Sl 720
5	3.5	P 720	C 720	Sl 720	Sl 720	P 720	P 720	Sl 720	P 720	Sl 720
6	3	P 720	C 20	C 20	C 720	C 720	C 720	P 305	C 720	C 720
7	3	P 316	C 8	C 8	Sl 109	∞	∞	∞	P 26	Sl 271
8	2.5	Sl 720	C 60	C 60	C 720	C 720	Sl 720	P 720	P 271	P 720
9	4	∞	P 720	P 720	Sl 720	Sl 720	Sl 720	Sl 720	P 720	Sl 720
10	2	Sl 720	C 720	P 60	Sl 720	∞	∞	∞	Sl 720	Sl 720
11	2	P 720	P 720	P 42	P 720	Sl 720	Sl 720	Sl 720	P 720	Sl 720
12	5	P 720	C 7	P 6	P 720	P 720	P 720	P 720	P 720	P 720
13	2	C 720	C 8	C 720	C 720	C 720	C 720	C 720	C 720	C 720
14	2	C 720	C 7	C 7	C 720	C 720	C 720	C 720	C 720	C 720
15	2.5	P 720	C 11	P 11	P 720	P 720	P 720	P 720	P 720	P 720
16	1	Sl 720	C 5	C 5	∞	∞	∞	∞	P 5	∞
17	1	∞	C 67	Sl 720	∞	∞	∞	∞	∞	∞
18	4	∞	C 9	Sl 720	∞	∞	∞	∞	∞	∞
19	1.5	∞	C 13	Sl 720	∞	∞	∞	∞	∞	∞
20	1	∞	C 13	C 13	∞	∞	∞	∞	Sl 720	∞
21	1	∞	C 38	∞	∞	∞	∞	∞	∞	∞
22	2.5	∞	C 720	∞	∞	∞	∞	∞	∞	∞

Nicotinic acid was added in the form of saturated solution (1%), in saline, the final concentration being 1.5 mg. per cc. of blood. Other acids were made up in normal saline and pH adjusted colorimetrically to duplicate that of the nicotinic acid solution.

In order to check on whether the observed effects were due simply to non-specific alteration of hydrogen-ion concentration, other acids were used (acetic, citric, lactic, oxalic, hydrochloric, nitric and sulphuric). These were made up in such concentrations as to duplicate the pH of the corresponding nicotinic acid solutions as determined colorimetrically. Comparison of the effect of these acids was made in a series of heparinized human blood samples (Table 2) and a series of samples from dogs in peptone shock (Table 3). Since the other acids used are all stronger than nicotinic acid, the final acidity of the blood mixtures would be greater than that attained with nicotinic acid. Nevertheless, only in an occasional instance in which acetic or nitric acids were used, was coagulation accelerated. This effect of these acids is probably to be attributed to their destructive action on the red cells, the stroma of which might well serve as mechanical foci from which clotting proceeds (Table 2).

**Discussion and Summary.** Clinical experience in a significantly large group of patients with chronic brucellosis revealed that nicotinic acid possesses the property of promoting coagulation of the blood. These patients often develop subcutaneous hemorrhages after slight trauma, and their blood clots slowly, retraction is imperfect, and the yield of serum is low. All of these defects were completely remedied by the administration of nicotinic acid.

These observations were extended to a small group of patients with other clinical states associated with bleeding, and the results were uniformly encouraging. Presumably, the hemorrhagic tendencies in all of these patients rested on a toxic, infectious basis. We have not as yet had opportunity to try this material in the various blood dyscrasias in which its possible effect would be of obvious interest and importance.

Experimental studies reported herein show that nicotinic acid does not duplicate the action of, nor can it be substituted for, any of the known factors involved in blood clotting (calcium, platelets, thromboplastic principle, prothrombin, or thrombin). However, when it is added *in vitro* to blood containing excessive amounts of antithrombin (heparinized blood or samples from dogs in peptone or anaphylactic shock), it does induce coagulation. That this effect is not due to non-specific alteration of hydrogen-ion concentration was indicated by contrast of nicotinic acid with seven other acids, none of which was as active in this respect as was nicotinic acid.

The quantities of nicotinic acid employed in our *in vitro* experiments were so enormous when compared with the doses used clinically, that it is not justifiable to assume that the mechanism of its effect in patients is necessarily a chemical neutralization of antithrombin, though such an explanation is possible. Certainly, in view of the small doses effective in patients, the results cannot be attributed to a non-specific acid effect. It would seem logical, we

believe, to conclude that nicotinic acid corrects a fundamental deficiency in the organism; or, by some pharmacodynamic action (*e. g.*, stimulation of the liver), induces the formation either of more prothrombin or of less antithrombin.

Whatever the mechanism of its action may be, our experiences indicate that further trial of nicotinic acid in various hemorrhagic states is warranted.

We are indebted to the S. M. A. Corporation, Chicago, for the nicotinic acid used in these experiments; and to Dr. R. L. Rhea of the San Antonio Veterinary Hospital for laboratory facilities.

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### CULTURE OF HUMAN MARROW.

STUDIES OF THE RELATIVE EFFECTIVENESS OF NEOARSPHENAMINE, MAPHARSEN, SULFANILAMIDE, SULFAPYRIDINE, SULFATHIAZOLE, AND SULFAMETHYLTHIAZOLE ON INFECTIONS WITH *STREPTOCOCCUS VIRIDANS* (ALPHA HEMOLYTIC *STREPTOCOCCUS*).<sup>\*†</sup>

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THE marrow culture method<sup>7</sup> is well adapted to controlled quantitative studies of the relative effectiveness of therapeutic agents on infections in the presence of living human cells.<sup>1,6a-c,e</sup> It seemed important to study the *Strep. viridans* because it is the major cause of subacute bacterial endocarditis, a disease with an almost 100% mortality, and because no reports were found in the literature which indicated that under controlled conditions any therapeutic agent in a concentration which would not kill human cells would

\* The drugs, except mapharsen and sulfapyridine, for this investigation were kindly supplied by the Department of Medical Research of the Winthrop Chemical Company, Inc.

† Presented before the Pacific Coast Surgical Association, Portland, Ore., April 4, 1940, and read by title at the meeting of the American Society for Clinical Investigation, Atlantic City, May 6, 1940.

lead to the death of these organisms. Neoarsphenamine, mapharsen, sulfanilamide, sulfapyridine, sulfathiazole and sulfamethylthiazole were chosen for study because of their known effectiveness against other organisms and because neoarsphenamine, sulfathiazole and sulfamethylthiazole have been found to be more effective in staphylococcus infections than sulfanilamide or sulfapyridine.<sup>6d-f</sup>

**Method.** Cultures of human bone marrow were prepared as previously described.<sup>7</sup> To about 50 cc. of culture containing about 100,000,000 nucleated marrow cells in one vial was added with syringe and needle a dilution of a culture in Hartley broth of *Strep. viridans*. After thorough mixing pour plates were made for colony counts, and equal volumes (about 8 cc.) were then transferred to each of a number of 30-cc. vaccine vials. This insured that each vial contained the same number of the same strain of organisms and the same number of cells in identical medium. To each of these, except the control, enough of the drug to be studied was added to give the desired concentration. The cultures were then placed in the incubator at 37° C., and pour plate counts and smears were made at intervals. This technique insures that the only variable is the presence of the drug.

TABLE 1.—COMPARATIVE EFFECTIVENESS OF DIFFERENT CONCENTRATIONS OF NEOARSPHENAMINE (STRAIN 3 IN TABLE 7).

	Hours:	Colony counts.			
		0.	6.	24.	96.
Control . . . . .	10	10	2500	300,000,000	
Neoarsphenamine,* 1:50,000 . . . . .	10	10	5?†	5?	0
Neoarsphenamine, 1:75,000 . . . . .	10	10	6?	0	0
Neoarsphenamine, 1:100,000 . . . . .	10	10	0	0	0
Neoarsphenamine, 1:200,000 . . . . .	10	10	15?	300	10
Neoarsphenamine, 1:400,000 . . . . .	10	10	100	100,000,000	

\* In concentrations greater than 1:75,000 the marrow cells were destroyed.

† In this and all subsequent tables the question mark indicates colony counts based on less than 20 or more than 500 colonies on a pour plate.

TABLE 2.—COMPARATIVE EFFECTIVENESS OF SULFANILAMIDE, SULFAPYRIDINE AND NEOARSPHENAMINE\* (STRAIN 4 IN TABLE 7).

	Hours:	Colony counts.		
		0.	6.	24.
Sulfanilamide, 1:10,000 . . . . .	20	20	>2500	10,000,000
Sulfapyridine, 1:20,000 . . . . .	20	20	>2500	8,000,000
Neoarsphenamine, 1:200,000 . . . . .	20	20	15	0

\* Note that neoarsphenamine was more effective than sulfanilamide and sulfapyridine.

**Results.** Examples of the results are shown in Tables 1 to 6 and in Figures 1 to 6. As has previously been shown<sup>5d-f</sup> concentrations of neoarsphenamine above 15 parts per 1,000,000 (or 1:70,000) killed all marrow cells, and concentrations of less than 2.5 parts per 1,000,000 (or 1:400,000) were ineffective in controlling infections. Concentrations of about 1:150,000 did not materially damage marrow cells and were very effective against most of the strains of *Strep. viridans*<sup>6d,e</sup> as shown in Tables 1 to 5. With the strains of organisms first tested, which gave results similar to those shown in Tables 2 and 3 and Figures 1 to 6, sulfanilamide, sulfapyridine and,

when tested, sulfathiazole and sulfamethylthiazole were relatively ineffective; whereas, neoarsphenamine and mapharsen were more effective. Preliminary reports based on these studies<sup>6d,e</sup> were made.

TABLE 3.—COMPARATIVE EFFECTIVENESS OF SULFAPYRIDINE, SULFATHIAZOLE, MAPHARSEN AND NEOARSPHENAMINE (STRAIN 5 IN TABLE 7).

	Hours:	Colony counts.		
		0.	26.	46.
Control . . . . .	2000	2000	8,500,000	100,000,000
Sulfapyridine, 1:10,000 . . . . .	2000	2000	4,000,000	100,000,000
Sulfathiazole, 1:10,000 . . . . .	2000	2000	7,000,000	100,000,000
Mapharsen, 1:2,000,000 . . . . .	2000	2000	1,500,000	100,000,000
Neoarsphenamine,* 1:10,000 . . . . .	2000	2000	0	

\* Due to an error in dilution a higher concentration of neoarsphenamine was used in this experiment than was intended. In several other experiments with this same strain neoarsphenamine in a concentration of 1:150,000 was effective. This experiment was selected, however, because a larger number of drugs were used or a greater number of colony counts were obtained than in the other experiments. See Figures 1 to 6 for the results of another experiment using this same strain. The patient from whom this culture was obtained has shown a good clinical response to therapy with neoarsphenamine and heparin, and she has had 5 negative blood cultures in the 6 weeks since therapy was discontinued.

TABLE 4.—COMPARATIVE EFFECTIVENESS OF SULFAPYRIDINE, SULFAMETHYLTHIAZOLE, SULFATHIAZOLE, NEOARSPHENAMINE, AND NEOARSPHENAMINE PLUS SULFATHIAZOLE\* (STRAIN 6 IN TABLE 7).

	Hours:	Colony counts.				
		0.	4.	24.	46.	48.
Control . . . . .	20	44	1,120,000	>100,000,000		
Sulfapyridine, 1:10,000 . . . . .	20	2?	0	....		0
Sulfamethylthiazole, 1:10,000 . . . . .	20	0	0	....		0
Sulfathiazole, 1:10,000 . . . . .	20	0	0	....		0
Neoarsphenamine, 1:150,000 . . . . .	20	4?	2?	....		0
Neoarsphenamine, 1:150,000 plus sulfathiazole, 1:20,000 . . . . .	20	0	0	....		0

\* All drugs were effective against this organism.

Subsequently, other strains were investigated (Tables 4 to 6) in which sulfapyridine, sulfathiazole and sulfamethylthiazole were also effective. One strain was found against which neoarsphenamine was

#### LEGENDS FOR FIGS. 1 TO 6.

FIG. 1.—Control at 28 hours from a marrow culture experiment in which the same strain of *Strep. viridans* as that shown in Table 3 was used (Wright's stain,  $\times 1200$ ). Compare this with Figures 2 to 6 which are from the same experiment and were taken at the same time.

FIG. 2.—Culture containing 1:10,000 sulfapyridine (Wright's stain,  $\times 1200$ ). Compare with Figures 1 and 3 to 6.

FIG. 3.—Culture containing 1:10,000 sulfathiazole (Wright's stain,  $\times 1200$ ). Compare with Figures 1, 2 and 4 to 6.

FIG. 4.—Culture containing 1:10,000 sulfamethylthiazole (Wright's stain,  $\times 1200$ ). Compare with Figures 1 to 3, 5 and 6.

FIG. 5.—Culture containing 1:1,500,000 mapharsen (Wright's stain  $\times 1200$ ). Compare with Figures 1 to 4 and 6.

FIG. 6.—Culture containing 1:150,000 neoarsphenamine (Wright's stain,  $\times 1200$ ). Compare with Figures 1 to 5. This is the only culture which became sterile. Note that the cells were undamaged.

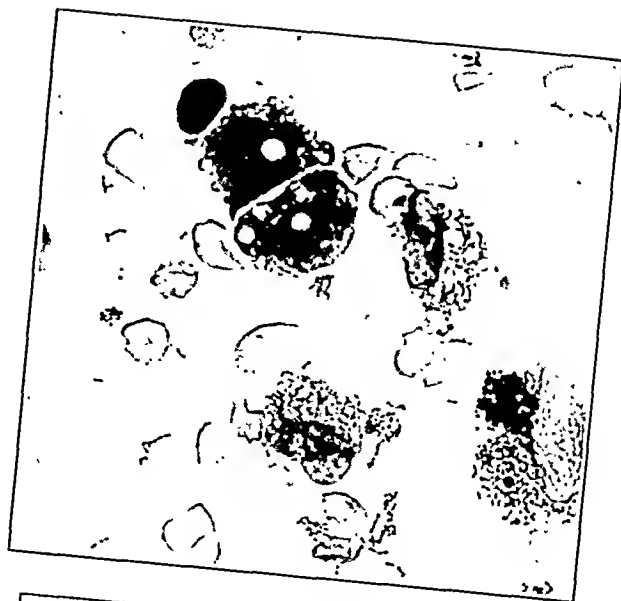


FIG. 1

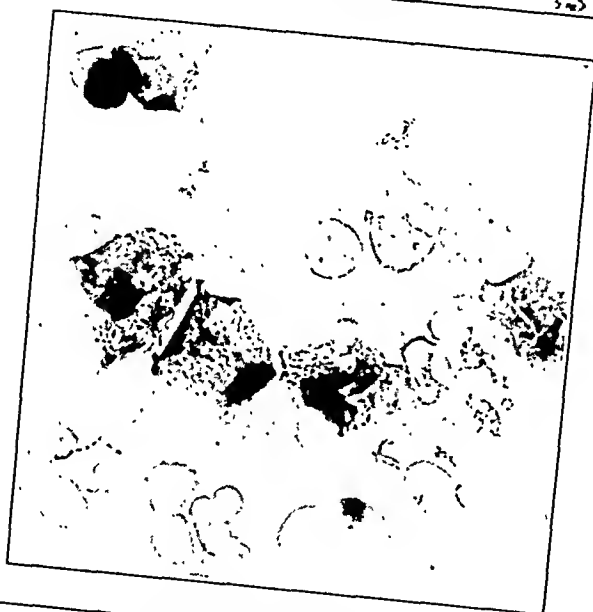


FIG. 2

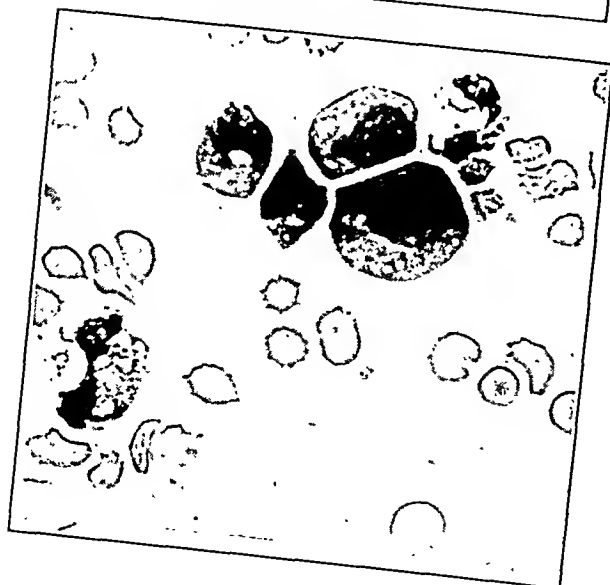


FIG. 3



FIG. 4



FIG. 5

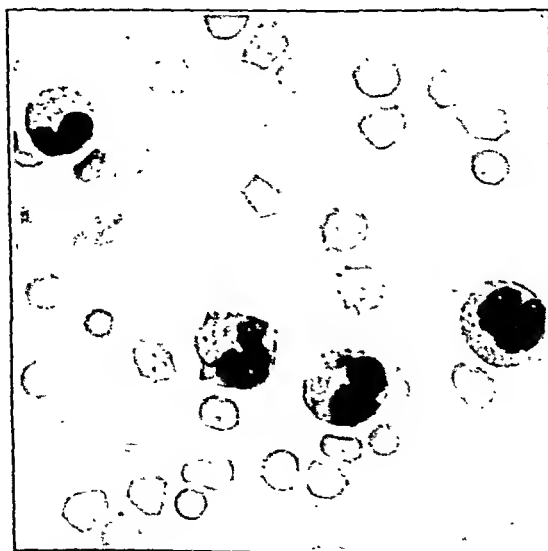


FIG. 6

tirely ineffective (Table 6). No cultural or morphologic characteristics were found which could distinguish the strains with different drug susceptibility from each other. Mapharsen in concentrations of 1:1,500,000 was as effective as neoarsphenamine in concentrations of 1:150,000 against some strains (Table 5) and not as effective against other strains (Table 3, Figs. 5 and 6). Sodium codylate and arsphenamine were not as effective as neoarsphenamine.

TABLE 5.—COMPARATIVE EFFECTIVENESS OF NEOARSPHENAMINE, MAPHARSEN, SULFATHIAZOLE AND SULFAMETHYLTHIAZOLE (STRAIN 7 IN TABLE 7).

	Hours:	Colony counts.				
		0.	4.	27.	48.	53.
Control . . . . .	50	200	6,000,000	>100,000,000		
Neoarsphenamine, 1:150,000 . . . . .	50	50	400	....		200,000
Mapharsen, 1:1,500,000 . . . . .	50	100	500	....		100,000
Sulfathiazole, 1:10,000 . . . . .	50	20	0		0	0
Sulfamethylthiazole, 1:10,000 . . . . .	50	40	0		0	0

TABLE 6.—COMPARATIVE EFFECTIVENESS OF NEOARSPHENAMINE, SULFAPYRIDINE, SULFATHIAZOLE AND SULFAMETHYLTHIAZOLE (STRAIN 8, TABLE 7).

	Hours:	Colony counts.			
		0.	4.	24.	70.
Control . . . . .	190	90	130,000?	>100,000,000	
Neoarsphenamine, 1:150,000 . . . . .	190	50	600,000	>100,000,000	
Sulfapyridine, 1:10,000 . . . . .	190	80	16		0
Sulfathiazole, 1:10,000 . . . . .	190	0	0		0
Sulfamethylthiazole, 1:10,000 . . . . .	190	300?	0		0

TABLE 7.—SUMMARY OF CHEMOTHERAPY ON DIFFERENT STRAINS OF *Strep. viridans* TESTED IN MARROW CULTURES.

Strains.	Sulfanilamide.	Sulfapyridine.	Sulfathiazole.	Sulfamethylthiazole.	Mapharsen.	Neoarsphenamine.	Neoarsphenamine plus sulfathiazole.
1	I	I					
2	I	I					
3*	...	...	...	...	...	S	
4	I	I	...	...	...	S	
5	...	III	III	I	III	SSSS	
6	...	SS	SSS	SS	I	SSI†	S
7	...	S	SSSS	SSS	E	EESE	S
8	...	S	S	S	...	I	
9	...	S	SESS	...	I	S	
10	...	SS	SS	...	I	E	
11	...	S	SE	SS	I	EE	

S, sterile; I, ineffective; E, effective (the colony counts were significantly lower than the counts in the control, or no organisms were found in the smears when the control was loaded).

\* Strains 3 to 8 correspond to the strains represented in Tables 1 to 6 in the same order.

† I, larger inoculation.

In addition to the 7 experiments on 6 strains illustrated in the tables and figures 1 to 4 experiments were done on each of 5 other strains listed, and the results of all experiments on each of the strains tested are summarized in Table 7.\* Sulfanilamide was ineffective

\* Since this article was submitted for publication many other strains have been investigated, each of which responded to neoarsphenamine alone, sulfathiazole and sulfapyridine alone, or to all three drugs, and a few strains were found which responded to sulfanilamide.



against each of the 3 strains tested; mapharsen was effective against 1 of the 5 strains tested; sulfapyridine, against 6 of the 10 strains tested; sulfathiazole against 6 of the 7 strains tested; sulfamethylthiazole, against 4 of the 5 strains tested; and neoarsphenamine, against 8 of the 9 strains tested. Neoarsphenamine and sulfathiazole in combination were effective against both of the two strains tested. Since neoarsphenamine was effective when sulfathiazole was not and *vice versa* the combination would probably have been effective against each of the strains tested.

**Comment.** It is evident that sulfanilamide is relatively ineffective against the *Strep. viridans*. Sulfapyridine is effective against some strains but is ineffective against others. It appears to offer no advantage over the more soluble and probably less toxic drug, sulfathiazole. Sulfathiazole and sulfamethylthiazole in concentrations of 1:10,000 are effective against many strains of *Strep. viridans* and are ineffective against other strains. In marrow cultures sulfathiazole and sulfamethylthiazole in equal concentration are equally effective, but it seems probable because of the lesser toxicity and greater solubility and greater ease in securing adequate blood concentration that sulfathiazole will prove clinically superior. Mapharsen is effective against some strains in the lowest concentration of any drug tested. Neoarsphenamine is effective against more of the strains tested than any of the other drugs investigated, but a concentration of about 1:150,000 (or 6 parts per 1,000,000) must be maintained constantly over a period of 24 to 72 hours or longer.

The development of an accurate method for blood arsenic by Raulston, Magnuson and Chaney<sup>9a,b</sup> made possible the calculation of the laws governing the distribution of the drug in the body and its elimination from the blood in man.<sup>6c</sup> After a single dose the drug is distributed evenly through the blood volume, but rapidly leaves the blood and after 2 to 3 hours is distributed almost evenly throughout the body tissues. From this time on the blood level drops comparatively slowly. During both periods the drug leaves the blood by a clearance mechanism which corresponds to a clearance of about 50 cc. of blood per hour. To maintain continuously the blood level desired of 1 part in 150,000 (or 130 gamma of arsenic per 100 cc.), as the results are reported, one should give  $\frac{1}{150,000}$  of the body weight in grams of neoarsphenamine  $\left( \text{or } \frac{\text{body weight in kg.}}{150} = \frac{\text{body weight in pounds}}{330} \right)$  the first day, divided into 3 or 4 spaced doses. Each subsequent day for 3 to 6 days give three-fourths of the total dose given on the first day, divided into 3 spaced doses. For example: If the body weight is 60 kg., give a total of 0.4 gm. in divided doses of 0.1 gm. each at 8 A.M., 11 A.M., 2 P.M., and 8 P.M.

Every subsequent day give 0.1 gm. at 8 A.M., 3 P.M., and 10 P.M. On the third day and subsequently at intervals, just before giving the 8 A.M. injection, take blood for blood arsenic determination.<sup>8,9</sup> Adjust the doses up or down as necessary to keep the blood arsenic level between 100 and 130 gamma per 100 cc. when the blood is taken at this time.

In a 70-kg. (or 150-pound) patient, a dose of 0.1 gm. will raise the blood level about 400 gamma immediately after and about 30 gamma 2 to 8 hours after administration. This rise will be inversely proportional to the weight and directly proportional to the dose; for example, if the blood level in a 30-kg. patient is 50 gamma at 8 hours, 0.1 gm. of extra neoarsphenamine will raise the level to about 110 gamma 2 to 8 hours after the next dose.

If the clinical effectiveness of the drugs is similar to their effectiveness in marrow cultures, as seems probable from the high correlation between clinical results and our previous culture studies of the effectiveness of drugs against other organisms,<sup>1,6a-c,e</sup> the following treatment for subacute bacterial endocarditis should be investigated. Since simple bacteriologic culture methods of differentiating the organisms which respond well to both sulfathiazole and neoarsphenamine from those which respond to sulfathiazole or neoarsphenamine alone have not yet been developed, unless marrow culture studies are available, a trial of neoarsphenamine alone should be made first because of its more frequent effectiveness. Give neoarsphenamine as outlined previously to maintain a blood level of 130 gamma of arsenic per 100 cc. If the temperature is not normal by the fourth day, give enough sulfathiazole or sulfapyridine every 4 hours to maintain a concentration of 8 to 10 mg. per 100 cc. Discontinue the neoarsphenamine if there was no effect on the temperature, and continue both drugs if the neoarsphenamine alone had reduced the temperature but not to normal. Clinical trial of such therapy should be controlled by daily search for evidence of toxicity from the drugs and by daily leukocyte counts and frequent hemoglobin, arsenic and sulfathiazole or sulfapyridine determinations. It is evident that this therapy alone will carry a certain mortality, but it would seem justifiable to run these risks in a disease with the high mortality of subacute bacterial endocarditis. Such studies are in progress and will be reported in a later paper,<sup>7</sup> but not enough time has elapsed to draw final conclusions, although the results so far obtained have been encouraging.

Since it has not been determined which of these drugs is the most effective in penetrating vegetations or if any of them will be able to kill organisms in the depths of vegetations, it would seem desirable for the present at least to continue the administration of the drug over a long enough period of time so that there may be a chance for it to penetrate to the center of the vegetations or, in any event, for healing on the surface and sufficient scar tissue contraction to occur

to imprison any organisms that remain. How long this period of time is has not yet been determined. However, it would seem desirable if toxicity is not encountered to continue the therapy for 60 days or longer in repeated courses of 3 to 6 days separated by 3- to 6-day rest periods. In the use of heparin intravenously, as suggested by Friedman, Hamburger and Katz,<sup>4</sup> and by Kelson and White,<sup>5</sup> there is a considerable risk of cerebral hemorrhage, and at most it can only hope to prevent deposition of new platelets and fibrin on the surface. It seems logical to believe that if the organisms near the surface are killed such deposition will cease in any event. Clinical trial of this therapy without heparin is in progress and will be reported in a later paper.<sup>8</sup>

The failure of neoarsphenamine or other organic arsenicals to give clinical cures in the cases in which they have previously been tried<sup>2</sup> may be explained by the fact that our studies show that a uniform low concentration of about 1:150,000 must be maintained in the blood stream for 24 to 72 hours, and probably much longer, to reach the center of a vegetation or allow time for fibrous tissue contraction; whereas, these drugs have been given previously in single large doses as in the therapy of syphilis. Obviously, much further work needs to be done by the marrow culture method to determine whether any other arsenical preparation is superior to neoarsphenamine, and to determine whether these drugs will penetrate a clot or a vegetation removed at necropsy, as well as much controlled clinical investigation to determine what is the ideal frequency of administration and dose of each drug and whether heparin is essential too.

**Summary.** In marrow cultures sulfanilamide in concentrations of 1:10,000 is relatively ineffective against *Strep. viridans*; sulfapyridine, sulfathiazole and sulfamethylthiazole in concentrations of 1:10,000 are ineffective against some strains but lead to sterility with other strains. Neoarsphenamine in concentrations of 1:150,000 is effective against more strains than any of the other drugs tested, but is less effective than sulfathiazole or sulfapyridine against some strains. Mapharsen deserves further study; in a concentration of 1:1,500,000 it is effective against certain strains, but is not as uniformly effective as neoarsphenamine in concentrations of 1:150,000. Carefully controlled clinical studies of the effectiveness of sulfathiazole or sulfapyridine in a dosage sufficient to maintain a blood level of 10 mg. per 100 cc. with neoarsphenamine given in intermittent courses of small frequently repeated doses with the objective of maintaining a blood level of about 1:150,000 should be made, with and without heparin given by continuous intravenous drip. Such studies have given encouraging results to date, but several more months must elapse after therapy was discontinued before a final report will be justified. It is hoped that similar studies will be undertaken in other institutions equipped for thor-

oughly controlled studies of this nature. In making such studies the risk of arsenical poisoning, agranulocytosis and other toxic effects of sulfathiazole and of hemorrhage from the heparin therapy must be kept constantly in mind.

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## QUICK'S PROTHROMBIN TEST SIMPLIFIED BY THE USE OF A STABLE THROMBOPLASTIN.

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SINCE Quick,<sup>4</sup> in 1935, introduced his prothrombin time test it has become widely used in the clinical investigation and control of the bleeding tendency of vitamin K deficiency which occurs in jaundice, hemorrhagic disease of the newborn, and other conditions.<sup>5</sup> The test measures the time taken for a sample of citrated plasma to coagulate, after recalcification, in the presence of an excess of tissue thromboplastin as compared with the time taken for a sample of normal citrated plasma to clot when treated in the same way. The test itself is extremely simple. The main reason that the practitioner

has difficulty in performing the test in his own laboratory is that it has heretofore been difficult to prepare the thromboplastin.

To perform the test as originally described by Quick, the thromboplastin is prepared from dried whole rabbit brain by saline extraction. The extract allows recalcified normal plasma to clot in 22 to 25 seconds, and retains its potency for about 4 days when kept at 5° C. In Quick's modification of his test,<sup>3</sup> the technique of which is the same and which is more commonly used at present, acetone-extracted brain substance is employed instead of dried whole rabbit brain. The saline extract prepared from acetone-extracted brain allows normal recalcified plasma to coagulate in 10 to 12 seconds and its activity begins to fall off 24 hours after its preparation.

Irrespective of which of these two thromboplastins is used, it is necessary to proceed with the rather laborious and time-consuming processes of removal and preparation of the brain, suspension, incubation and centrifugation of its saline extract. The necessity for having a high-powered centrifuge is alone sufficient to make the performance of the test impracticable for many whose office does not contain this piece of apparatus.

The introduction therefore of a stable thromboplastin requiring for its complete preparation no more than the addition of distilled water is desirable. This would greatly simplify the procedures involved in the carrying out of the Quick prothrombin test. At the suggestion of Dr. F. H. L. Taylor<sup>7</sup> we attempted the preparation of a stable thromboplastin by utilizing the method of "lyophilization" introduced by Flosdorf and Mudd.<sup>1</sup> A preliminary report of this preparation has been published.<sup>6</sup> The details of the preparation of such a stable thromboplastin suitable for general use in the Quick prothrombin test are presented below.

**Methods.** For reasons which will appear later, we preferred to use the original Quick procedure, using thromboplastin from dried whole rabbit brain.<sup>4</sup> Brains were removed from freshly-killed rabbits and the larger superficial blood-vessels stripped off after washing with water. The brains were then ground to a paste, spread thinly on a glass plate and thoroughly dried in an oven at 37° C. The dried residue was scraped off the plate and about 15 cc. of saline extract were prepared by adding 30 cc. of 0.85% sodium chloride solution to 3 gm. of dried brain, mixing with a glass rod and incubating at 56° C. for 15 minutes. On centrifuging the mixture at 2000 r.p.m. for 5 minutes, a somewhat opalescent supernatant fluid was obtained. About 2 cc. of this extract were set aside for testing as a control and the remainder placed in small serum bottles, 1 cc. in each. The contents of these bottles were then "lyophilized" and at the completion of the process the evacuated bottles were set aside for storage at room temperature (about 20° C.).

The portion of extract which was kept as a control was tested for thromboplastic activity by using it to determine the Quick prothrombin times of a series of dilutions of normal citrated plasma with prothrombin-free plasma prepared by the method of Kark and Lozner<sup>2</sup> so that the preparations contained 100%, 80%, 60%, 40%, 20% and 0% prothrombin (Table 1).

The technique used in the determination of these prothrombin times was essentially that of Quick.<sup>4</sup> One-tenth cubic centimeter of thromboplastin was pipetted into a tube 10 by 75 mm. and the tube placed in a constant temperature (37.8° C.) water-bath. After a few minutes 0.1 cc. of plasma was added and immediately thereafter 0.1 cc. of 0.277% solution of calcium chloride. At the moment of delivery of the calcium chloride solution from the pipette a stop-watch was started. The tube was agitated gently in the bath for 15 seconds and then rocked while held in the air until the contents ceased to flow freely. At this point the watch was stopped and the time taken.

Bottles containing the dry, powdered, "lyophilized" material were opened at intervals of 1, 2, 3, 4, and 10 weeks after "lyophilization" and the contents restored to their original volume by the addition of distilled water, when a somewhat opalescent solution was readily obtained. The thromboplastic activity was then determined on each occasion by testing against plasmas containing various percentages of prothrombin. At the same time the results obtained were compared with those given by an extract freshly made up from the original dried rabbit brain substance stored in the ice box at 5° C. The figures for these results are shown in Table 1.

TABLE 1.—THE QUICK PROTHROMBIN TIME OF MIXTURES OF NORMAL AND PROTHROMBIN-FREE PLASMAS USING FRESHLY PREPARED AND LYOPHILIZED THROMBOPLASTINS.

Time in weeks after lyophilization of throm- boplastin at which Quick prothrombin times were observed.		Quick prothrombin times of mixtures of normal plasma and prothrombin-free plasma (seconds).					
		Percentage of normal plasma in mixtures.					
		100%.	80%.	60%.	40%.	20%.	0%.
Fresh thromboplastin extract for lyophilization . . . . .	Control	21	23	26	29	40	No clot
"Lyophilized" thromboplastin	1	21	24	27	32	50	"
Freshly prepared thromboplastin	1	20	21	23	28	42	"
"Lyophilized" thromboplastin	2	24	26	28	34	56	"
Freshly prepared thromboplastin	2	23	25	26	32	52	"
"Lyophilized" thromboplastin	3	23	25	28	34	54	"
Freshly prepared thromboplastin	3	21	23	25	29	45	"
"Lyophilized" thromboplastin	4	21	24	26	31	49	"
Freshly prepared thromboplastin	4	20	22	25	30	40	"
"Lyophilized" thromboplastin	10	21	23	25	33	68	"
Freshly prepared thromboplastin	10	21	23	26	33	68	"

**Discussion.** From Table 1 it will be seen that practically no loss of thromboplastic activity occurred in the process of "lyophilization" of the extract from dried whole rabbit brain and that storage of the evacuated bottles at room temperature over as long a period as 10 weeks caused no depreciation in potency. This is in contrast to the fresh saline extract of rabbit brain which retains potency for only a few days. Thus by this method an active thromboplastic material was obtained ready for immediate use on the addition of distilled water alone.

Availability of the thromboplastic substance in evacuated ampoules would seem to remove the one serious obstacle to the performance of the Quick prothrombin test in the physician's office and permits it to be performed with greater ease anywhere. The other reagents, sodium oxalate or citrate and calcium chloride are readily available; a water-bath at 37° C. can be improvised without

difficulty or indeed can be dispensed with entirely and the test carried out at room temperature provided that the patient's plasma and that of the normal control are treated identically. Enough dry thromboplastin for 9 tests is obtained by the "lyophilization" of a single cubic centimeter of saline extract from rabbit brain. To prepare from this dried material thromboplastin solution for immediate use in the test, all that is necessary is to add sufficient distilled water to make up the original volume.

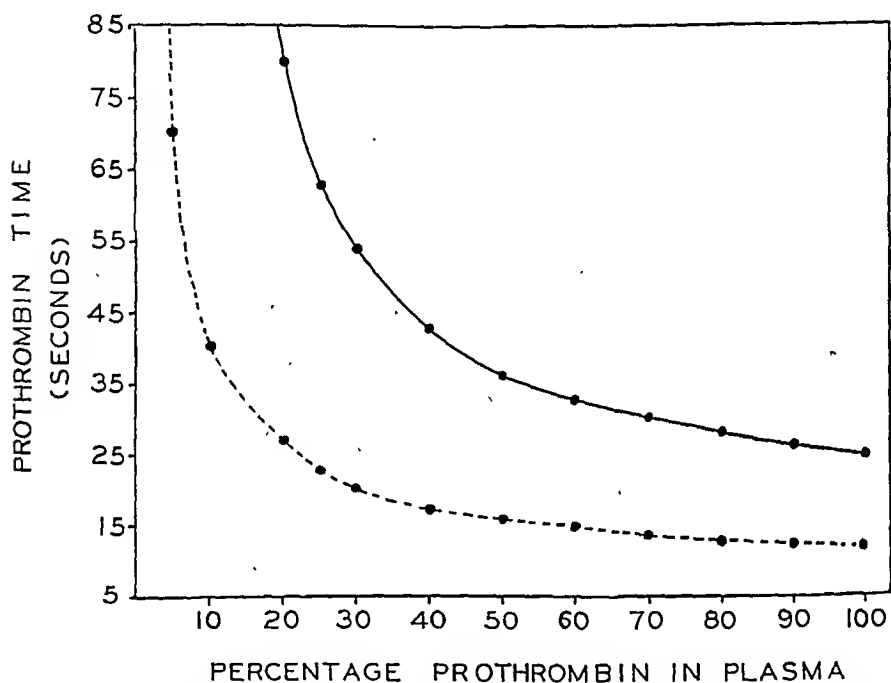


CHART 1.—The relation between the prothrombin percentage of human plasma and the Quick "prothrombin time" in the presence of Quick's original thromboplastin (solid line) and Quick's modified thromboplastin (broken lines).

The original test of Quick using thromboplastin from whole dried rabbit brain was employed in preference to his modification using thromboplastin from acetone-extracted brain. This is chiefly because of the extreme potency of the thromboplastic extract used in the latter modification of the test. So strong are its clot-accelerating powers that even with quite definite reduction in the blood prothrombin level only very slight prolongation of the prothrombin time occurs and it is not until dangerously low levels of prothrombin are reached that any marked change is noted in the prothrombin time.

A graphic comparison of the potencies of the two thromboplastic extracts derived from whole rabbit brain and acetone extracted

brain, respectively, is shown in Chart 1. In a test such as this, when the time of a reaction represents the concentration of one interacting substance, it is essential for accurate estimation of the amount of that substance present, that decrease in its concentration should be reflected by an appreciable prolongation of the time of the reaction. It is notable that a rise of 5 seconds in the prothrombin time when the first extract is used indicates a fall in prothrombin level to 70% of normal, while this amount of lengthening of the prothrombin time when the second extract is employed does not occur until the prothrombin concentration is as low as 50% of normal. When the "hemorrhagic level" (30% to 35% of normal) is reached the extract from dried whole rabbit brain permits a striking prolongation of prothrombin time (from 25 up to 50 seconds) while the more potent extract shows a rise only from 12 to about 18 seconds for an identical fall in the prothrombin level. It is therefore possible to make a more accurate estimation of the active prothrombin content of plasma by using the saline extract from dried whole rabbit brain, especially when the prothrombin concentration is reduced to a moderate degree, barely appreciable when the more potent extract is used. This is extremely important clinically, for instance, preoperatively in certain jaundiced patients, in whom a reduction of blood prothrombin to perhaps 70% of normal might pass unnoticed if the more potent thromboplastin were used, as it would be indicated by a prolongation of only 2 seconds in the prothrombin time over that of a normal control. If operation were carried out in such patients at this stage, without therapy with vitamin K, then a farther small drop in blood prothrombin as a result of operative procedures might well bring it to the hemorrhagic level with serious and possibly fatal results.

**Summary.** A method is described for the preparation of a stable thromboplastin suitable for use in the Quick prothrombin test. The material is ready for immediate use on the addition of distilled water alone, thus permitting of the performance of the test by the physician in his office, and allowing it to be carried out with greater ease anywhere.

Reasons are given for employing a relatively weak thromboplastin as prepared originally by Quick in preference to the potent thromboplastin which he introduced later.

The authors gratefully acknowledge the technical assistance of Nancy deFritsch, A.B.

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## THE MECHANISM OF RENAL HYPERTENSION.

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THE coexistence of arterial hypertension with pathologic changes in the kidneys has been known for a long time. Experimental studies indicated that hypertension could be produced by vascular alterations in the kidney, but increases in blood pressure were not consistent and of short duration. Systematic studies have only become possible with the discovery of Goldblatt, Lynch, Hanzal and Summerville,<sup>9</sup> that incomplete renal ischemia produces a marked and permanent arterial hypertension. This discovery has opened a new field in experimental studies, since the condition so caused in the dog and other animals is similar to human hypertension. It has thus been possible to prove the humoral mechanism of renal hypertension and to discover the presence of a pressor substance in the venous blood of ischemic kidneys. This substance can also be prepared *in vitro* and although its chemical constitution is still unknown its formation and mode of action have been studied. Our present knowledge of the mechanism of renal hypertension might be summarized as follows: Renal ischemia determines the secretion of "renin." This protein is an enzyme which acts on a blood globulin ("hypertensin precursor") and gives rise to a substance ("hypertensin") which produces vasoconstriction. Another enzyme "hypertensinase" which destroys hypertensin, is present in blood and tissues.

**A. The Presence of a Pressor Substance in Venous Blood of Ischemic Kidneys.** Experiments which prove that a pressor substance is secreted by ischemic kidney have been performed with: (a) kidneys from hypertensive dogs with chronic ischemia; (b) kidneys after complete ligation of the renal artery; and (c) kidneys after partial acute ischemia.

(a) Houssay and Fasciolo<sup>16</sup> found that if the ischemic kidney of a dog with chronic hypertension was grafted to the neck of a normal or nephrectomized dog, an increase in blood pressure was produced. This rise was prolonged and persisted for some time after the removal of the graft. It was more pronounced in nephrectomized than in normal dogs and not produced by grafting a normal kidney. Dicker,<sup>4a</sup> and Bouckaert, Grimson and Heymans<sup>1</sup> obtained

similar results. Houssay and Taquini<sup>17</sup> found that the citrated plasma obtained from the veins of ischemic kidneys produced vasoconstriction when perfused through a toad's hind limbs (Läwen-Trendelenburg preparation). Pressor activity has also been demonstrated in the systemic blood of hypertensive dogs. In the experiments of Solandt, Nassim and Cowan<sup>28</sup> an exchange transfusion of systemic blood was established between a hypertensive dog and a nephrectomized dog. A transient hypertension was observed in the latter.

(b) If after some hours of complete ischemia of normal kidneys the circulation is reestablished a rise in blood pressure is observed in the same dog or in the recipient with the grafted kidney.<sup>4b,27,30a,b</sup> Vasoconstriction was observed when the citrated plasma was perfused through the Läwen-Trendelenburg preparation.<sup>30b</sup>

(c) Acute partial ischemia of a few minutes is sufficient to produce the appearance of a pressor and vasoconstrictor activity in the venous blood of normal kidneys.<sup>2a,5,10,22</sup>

The pressor activity of this blood was not modified by section of the vagi, denervation of the carotid sinus, adrenalectomy, or the injection of cocaine, atropine or Fourneau 933.<sup>2b,3b</sup> The vasoconstrictor activity of this blood was also revealed by the Läwen-Trendelenburg preparation or by the perfusion through denervated hind limbs of dogs.<sup>2b,3b</sup> It was found that the pressor substance of the venous blood of ischemic kidneys remained in solution after adding three volumes of acetone, that it was thermostable and insoluble in ether and amyl alcohol. Some of the chemical and pharmacologic properties of this substance were studied and as they did not correspond to any known pressor substance, it was named hypertensin.<sup>3a,b,18</sup>

It was later found<sup>22</sup> that hypertensin is formed in the blood. Ischemic kidneys secrete renin,<sup>20,22</sup> which acting upon blood globulins gives rise to hypertensin. If the venous blood of ischemic kidneys is collected in acetone or rapidly cooled no hypertensin is found in the extracts. It is found only after the blood has been incubated for a certain time. This generation of hypertensin is due to the action of renin as is shown in the following paragraph.

**B. Renin.** In 1898, Tigerstedt and Bergmann<sup>31</sup> discovered that kidney extracts contained a pressor substance: renin, which was not found in extracts of other organs. Subsequent studies<sup>11,13,14,26</sup> showed that the active substance was a protein, and probably a globulin inactivated by heat 60° C. The purification of renin has been lately studied by Swingle, Taylor, Collings and Ways.<sup>29</sup> A specimen that they kindly sent to us was found to be practically free from cathepsin and hypertensinase.<sup>22</sup>

The intravenous injection of renin produces a gradual rise in blood pressure which lasts from 10 to 30 minutes, depending on the dose. The effect is not modified by vagotomy, denervation of

the carotid sinus, pithing, or injection of atropine, cocaine or Fournau 933. Nephrectomized dogs are more sensitive to renin,<sup>3b</sup> and adrenalectomized and hypophysectomized rats are less sensitive.<sup>33</sup> Consecutive injections of large doses at short intervals produce each time a smaller response but the continuous injection of small amounts produces a sustained elevation of blood pressure.<sup>15</sup>

The pressure increase produced by renin is not direct but occurs by the intermediation of hypertensin. The perfusion of renin in Ringer solution through a vascular system: dog's tail,<sup>21</sup> or Lâwen-Trendelenburg preparation,<sup>3b</sup> does not produce vasoconstriction. If renin is diluted in citrated plasma or horse serum instead of Ringer's solution and perfused after short incubation, marked vasoconstriction results, due to the hypertensin formed. The plasma or serum must be previously tested alone, to discard any vasoconstrictor action ("Spätgift," vasoconstrictin).

The elevation of blood pressure has been generally used as a test for the activity of renin. The relation between blood pressure rise and dose has been studied by Swingle, Taylor, Collings and Ways.<sup>29</sup> The formation of hypertensin can also be used as a test. When renin is added to serum at 37° C. hypertensin is formed, as can be shown by testing the pressor action of the alcoholic extracts. With this method it is possible to detect quantities of renin 50 to 100 times smaller than by direct injection.

For instance, 2 cc. of one of our renin solutions were needed to increase the pressure of a 10 kg. dog by 30 mm. Hg. If 0.05 cc. of the same solution were incubated with 10 cc. blood globulins, the following pressure increases were obtained on injection of the extract to the same dog.

Time of incubation in minutes . . . . .	0	5	15	30	60
Pressure rise in mm. Hg . . . . .	10	24	34	52	54

However, this method can only be used with purified preparations because if hypertensinase is present, the hypertensin is destroyed.

There are several reasons for considering renin as an enzyme and blood globulins as the substrate. Renin is a protein and its activity is destroyed by heating. The yield of hypertensin is proportional to the amount of globulins. If the amount of renin exceeds the optimum, the maximum yield is not surpassed using 10 or 20 times more renin; the results obtained when a fixed amount of serum without hypertensinase is incubated with varying amounts of renin are shown in Figure 1. The maximum yield of hypertensin is attained in less than 15 minutes with 0.1 cc. and only in 2 hours with 0.05 cc. If the reaction were stoichiometric, the maximum amount of hypertensin formed ought to be proportional to the amount of renin.

Since the substrate on which renin acts is a protein and the reaction product is probably a polypeptide, it is reasonable to class renin

as a proteolytic enzyme. The pH optimum for the reaction was found to be between 7.5 and 8.5 (Fig. 2). The formation of hypertensin is not inhibited by cyanide, fluoride, octyl alcohol, thymol

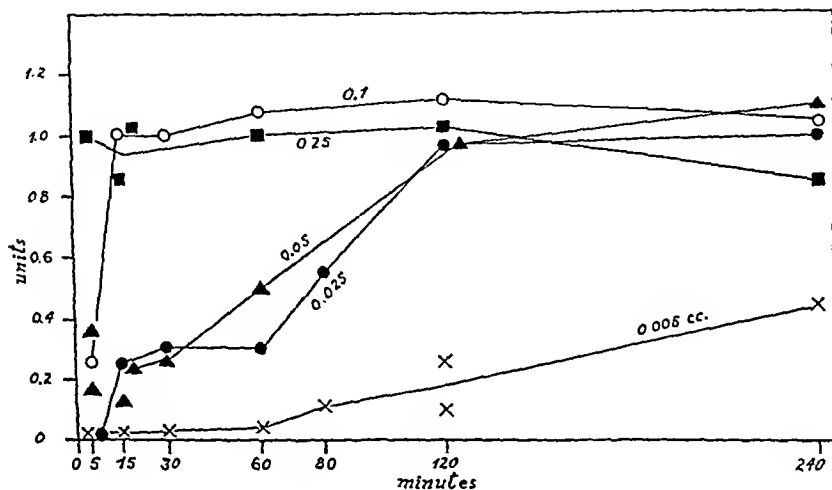


FIG. 1.—Units of hypertensin formed by incubating 10 cc. of bovine plasma—treated so as to destroy hypertensinase—with different amounts of renin solution during variable times. Temperature, 37° C. Hypertensin as estimated by comparing the pressure increases produced in chloralosed dogs with a standard solution.  $\times$  0.005 cc. renin,  $\bullet$  0.025 cc.  $\blacktriangle$  0.05 cc.  $\circ$  0.1 cc.  $\blacksquare$  0.25 cc.

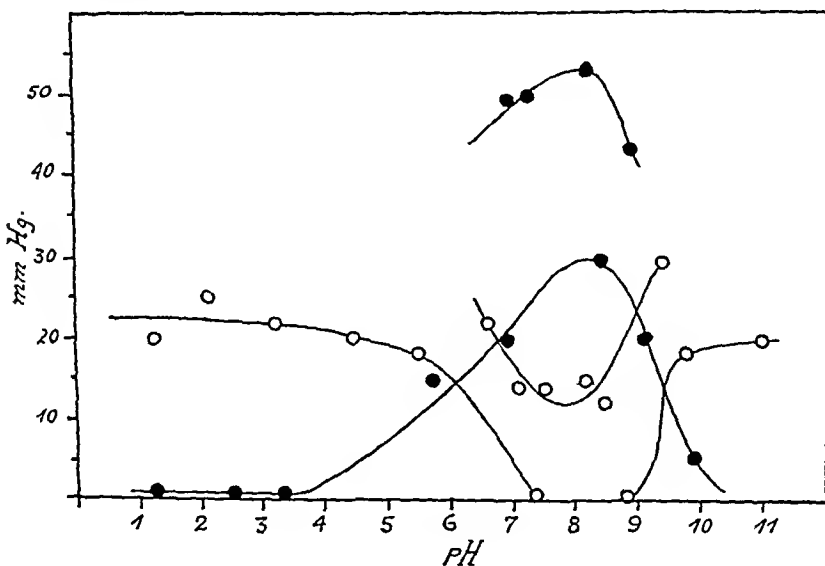


FIG. 2.—pH activity curve of renin and hypertensinase. Black dots: blood pressure increases produced by injecting the extract of 10 cc. blood globulin solution incubated with 0.25 cc. renin for 15 minutes. Each curve corresponds to one experiment. White dots: lower curve: extracts from 10 cc. ox-blood plasma incubated 80 minutes with 0.5 cc. hypertensin solution. Upper curve: another experiment with 50 minutes' incubation. Reaction temperature, 37° C. pH adjusted with HCl or NaOH and measured in an aliquot part with a glass electrode.

or toluol. Extracts of other organs (liver or spleen) do not produce hypertensin when incubated with blood globulins and other enzymes; pepsin, trypsin and papain were also found ineffective.

Renin is usually prepared from pigs' kidneys. This renin was found to be active on pig, ox, horse and dog serum, but no hypertensin was formed when it was incubated with human serum. On the other hand, renin prepared from human kidneys was active on any of these sera.<sup>8</sup> These results suggested that the injection of pig's renin would not produce a blood pressure increase in human subjects and this was found to be the case in the patients tested. The injection of human renin gives a pressure increase in human subjects (Battro and Lanari, unpublished results).

**C. Hypertensin Precursor.** The substance in blood serum on which renin acts to form hypertensin has been called hypertensin precursor or hypertensinogen. This is the substance which was found by Kohlstaedt, Helmer and Page<sup>21</sup> to produce vasoconstriction when mixed with renin. They call it renin-activator. However, as experiments indicate that it is the substrate of the enzyme renin, the name "renin-activator" does not appear to be desirable. It is precipitated from blood serum by half saturation with ammonium sulphate, by saturated sodium chloride at pH 2 to 3, potassium phosphate 2 M,<sup>24</sup> inactivated by heat and not precipitated by dialysis. Its properties correspond therefore to those of a pseudoglobulin.

Attempts to obtain it from other sources than blood serum have failed; liver, spleen, thymus, testes, lungs, heart or skeletal muscle, milk and egg proteins, hemoglobin, serum albumin and some vegetable proteins did not yield hypertensin when incubated with renin.

The hypertensin precursor can be estimated in blood samples by the maximum amount of hypertensin that it produces. It is necessary to use a renin preparation which is free from hypertensinase. This can be obtained by precipitating renin preparations with 25% NaCl at pH 2 to 2.5. Under these conditions hypertensinase is destroyed. In order to prevent the action of the hypertensinase of serum, the incubation period should be short (5 to 10 minutes) and therefore a large excess of renin is necessary.

The amount of renin to be employed was determined for each preparation as follows: 10 cc. of oxalated blood plasma (ox) were incubated at 37° C. with different amounts of renin during variable times. Three volumes of alcohol were added; after filtration and evaporation of the alcohol, the samples were injected into a chloralosed dog (Table 1). In this case 0.25 cc. was a sufficient amount of renin to produce the maximum yield of hypertensin in 5 minutes. After an incubation of 40 minutes, the hypertensinase in the plasma had destroyed all the hypertensin formed and no increase in blood pressure occurred. The pressure rises can be compared with those produced by a standard hypertensin solution.

TABLE 1.—RISE IN BLOOD PRESSURE FOLLOWING INTRAVENOUS INJECTIONS OF EXTRACTS OF BLOOD GLOBULINS INCUBATED WITH RENIN.

Cc. renin.	Increase of blood pressure in mm. Hg, time of incubation.		
	5 min.	15 min.	40 min.
0.25 . . . . .	20	22	
0.5 . . . . .	24	20	
1.0 . . . . .	20	14	
2.5 . . . . .	20	20	0

TABLE 2.—CHANGES IN HYPERTENSION PRECURSOR PRODUCED BY INTRAVENOUS INJECTION OF RENIN.

	Blood pressure increases in mm. Hg.							
	55	30	45	55	50	40	22	120
Before renin . . . . .	55	30	45	55	50	40	22	120
After renin . . . . .	0	15	0	25	0	5	5	50

Samples of blood serum (7 to 18 cc.), taken before and 15 to 30 min. after injecting renin (0.5 to 1 cc. per kg.) into a dog, were incubated with an excess of renin for 10 minutes at 37° C. The alcoholic extracts were injected to a chloralosed dog. Each column records a different experiment.

Using this method some changes in the hypertensin precursor content of blood under different conditions were studied. After the injection of renin to chloralosed dogs, the hypertensin precursor decreases and even disappears from blood (Table 2 and Fig. 3).

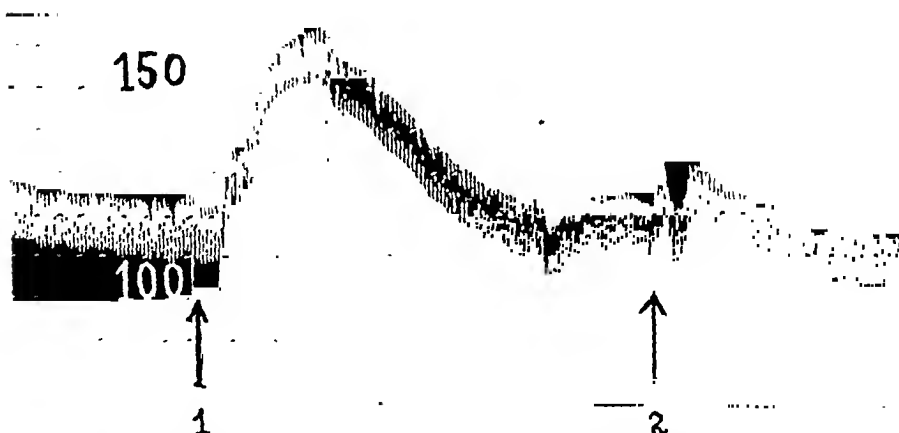


FIG. 3.—Hypertensin precursor in the blood of a 10 kg. dog before (1) and after (2) injection of 0.5 cc. renin per kg.; 10 cc. samples of serum incubated 10 minutes with an excess of renin. Rise in blood pressure observed by injection of alcoholic extracts to a chloralosed dog.

After nephrectomy, the hypertensin precursor increases. A sample of blood serum was obtained before and 48 hours after double nephrectomy in dogs. The precursor was estimated as described with the results shown in Table 3.

The increase in hypertensin precursor after nephrectomy may be explained by assuming that the kidney secretes normally small

amounts of renin which decompose some of the hypertensin precursor. It has also been found that there occurs a decrease in hypertensinase after nephrectomy (see below). The extent to which this change may affect the estimation of precursor has not been yet ascertained.

TABLE 3.—CHANGES IN HYPERTENSIN PRECURSOR, PRODUCED BY NEPHRECTOMY IN DOGS.

	Rise in blood pressure, mm. Hg.					
Before nephrectomy . . . . .	90	18	15	20	18	94
48 hours after nephrectomy . . .	102	25	30	35	38	120

Samples of plasma were incubated with an excess of renin for 5 minutes at 37° C. and the extract tested for pressor activity in a chloralosed dog. Each column records 1 experiment.

**D. Hypertensin.** The incubation of renin with blood globulins gives rise to a pressor substance which has the same chemical and pharmacologic properties as the substance found in the venous blood of ischemic kidneys. This substance was named hypertensin.<sup>3a,b,23</sup> Experiments by Page and Helmer<sup>24</sup> led to the independent discovery of the same substance, which they named angiotonin. Page and Helmer report obtaining a crystalline picrate and oxalate. No melting point or elementary composition are mentioned.

Hypertensin is very soluble in water and soluble in glacial acetic acid, liquid phenol, ethylene glycol, only slightly soluble in absolute alcohol, insoluble in ether and butyl or amyl alcohol. It is resistant to acids (2 hours in HCl 1 n at 100° C.) but sensitive to alkali. It can be salted out by ammonium sulphate. It dialyzes through cellophane. It is inactivated by incubation with pepsin. Although Page and Helmer report that the biuret reaction is negative, the inactivation by pepsin (Fig. 4) would indicate that it is a polypeptide.

The method of preparation which we used was as follows: Dialyzed blood globulins were allowed to react with renin and then precipitated with three volumes of alcohol. The filtrate was evaporated *in vacuo* and extracted with ether. The solution was then either treated again with alcohol or dried, extracted with glacial acetic acid and precipitated with ether. Hypertensin can be extracted with phenol from aqueous solutions after saturating them with ammonium sulphate. The active substance can then be extracted by water after the addition of 2 volumes of ether.

A unit of hypertensin was regarded as the amount which gives a blood pressure increase of 20 to 30 mm. Hg in a 10 kg. chloralosed dog. About 1 unit is obtained from 10 cc. bovine serum. The blood pressure increase lasts 3 to 4 minutes and is roughly proportional to the amount injected, as was shown by Braun-Menendez, Fasciolo, Leloir and Muñoz.<sup>3b</sup>

Even after 15 to 20 injections, the injection of equal amounts produce equal effects; there is therefore no tachyphylaxis to hypertensin. The pressor action is not modified by previous injection of

Fourneau 933; it is reinforced by cocaine and specially by "veritol." Continuous injection of hypertensin (1 unit per minute) produces a sustained elevation similar to that produced by a single dose of renin. The pressor effect is not modified by double section of the vagi, pithing, adrenalectomy, denervation of the carotid sinus.<sup>3a,b</sup>

Hypertensin produces a marked vasoconstrictor action on the L wen-Trendelenburg preparation (0.25 to 0.5 units in 100 cc. Ringer solution). A decrease in volume of the spleen and kidney was found after injection into the jugular vein of dogs. The heart rate was not modified in vagotomized dogs, in the heart lung preparation or in the isolated toad heart. Intravenous injection of hypertensin did not induce contraction of the retractor penis in pithed dogs; with high doses a slow contraction of the nictitating

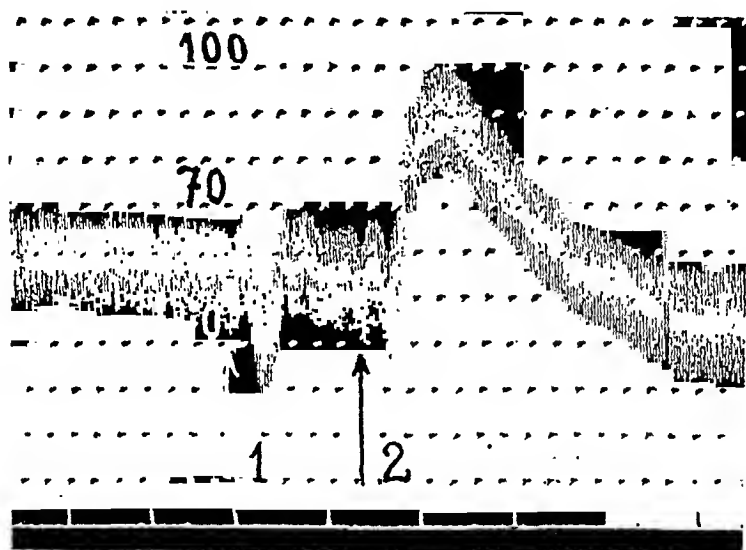


FIG. 4.—1, One unit of hypertensin incubated with pepsin at pH2. 2, The same with boiled pepsin solution. Alcoholic extracts injected to a chloralosed dog.

membrane was observed in chloralosed cats. In small doses (1 unit in 1000 cc. Ringer solution) it increased the height of contraction and the tonus of isolated rat or guinea pig uterus (which are inhibited by epinephrin), it stimulated contraction of rabbit uterus (as does epinephrin), it increased the tone of rat's gut (as does acetylcholine) and this action was not inhibited by atropine (Ludue a, unpublished results).

**E. Hypertensinase.** When blood serum is incubated with renin, the amount of hypertensin increases rapidly, then decreases and finally disappears.<sup>3a,b,24</sup> This disappearance is produced by serum and also by renin if impure preparations are used.

If 1 unit of hypertensin is incubated with 2 cc. of dog's serum (total volume, 2.5 cc.) at 37  C., the activity disappears gradually.



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Before nephrectomy . . . . .	90	18	15	20	18	94
48 hours after nephrectomy . . .	102	25	30	35	38	120

Samples of plasma were incubated with an excess of renin for 5 minutes at 37° C. and the extract tested for pressor activity in a chloralosed dog. Each column records 1 experiment.

**D. Hypertensin.** The incubation of renin with blood globulins gives rise to a pressor substance which has the same chemical and pharmacologic properties as the substance found in the venous blood of ischemic kidneys. This substance was named hypertensin.<sup>3a,b,23</sup> Experiments by Page and Helmer<sup>24</sup> led to the independent discovery of the same substance, which they named angiotonin. Page and Helmer report obtaining a crystalline picrate and oxalate. No melting point or elementary composition are mentioned.

Hypertensin is very soluble in water and soluble in glacial acetic acid, liquid phenol, ethylene glycol, only slightly soluble in absolute alcohol, insoluble in ether and butyl or amyl alcohol. It is resistant to acids (2 hours in HCl 1 n at 100° C.) but sensitive to alkali. It can be salted out by ammonium sulphate. It dialyzes through cellophane. It is inactivated by incubation with pepsin. Although Page and Helmer report that the biuret reaction is negative, the inactivation by pepsin (Fig. 4) would indicate that it is a polypeptide.

The method of preparation which we used was as follows: Dialyzed blood globulins were allowed to react with renin and then precipitated with three volumes of alcohol. The filtrate was evaporated *in vacuo* and extracted with ether. The solution was then either treated again with alcohol or dried, extracted with glacial acetic acid and precipitated with ether. Hypertensin can be extracted with phenol from aqueous solutions after saturating them with ammonium sulphate. The active substance can then be extracted by water after the addition of 2 volumes of ether.

A unit of hypertensin was regarded as the amount which gives a blood pressure increase of 20 to 30 mm. Hg in a 10 kg. chloralosed dog. About 1 unit is obtained from 10 cc. bovine serum. The blood pressure increase lasts 3 to 4 minutes and is roughly proportional to the amount injected, as was shown by Braun-Menendez, Fasciolo, Leloir and Muñoz.<sup>3b</sup>

Even after 15 to 20 injections, the injection of equal amounts produce equal effects; there is therefore no tachyphylaxis to hypertensin. The pressor action is not modified by previous injection of

Fourncau 933; it is reinforced by cocaine and specially by "veritol." Continuous injection of hypertensin (1 unit per minute) produces a sustained elevation similar to that produced by a single dose of renin. The pressor effect is not modified by double section of the vagi, pithing, adrenalectomy, denervation of the carotid sinus.<sup>3a,b</sup>

Hypertensin produces a marked vasoconstrictor action on the Låwen-Trendelenburg preparation (0.25 to 0.5 units in 100 cc. Ringer solution). A decrease in volume of the spleen and kidney was found after injection into the jugular vein of dogs. The heart rate was not modified in vagotomized dogs, in the heart lung preparation or in the isolated toad heart. Intravenous injection of hypertensin did not induce contraction of the retractor penis in pithed dogs; with high doses a slow contraction of the nictitating

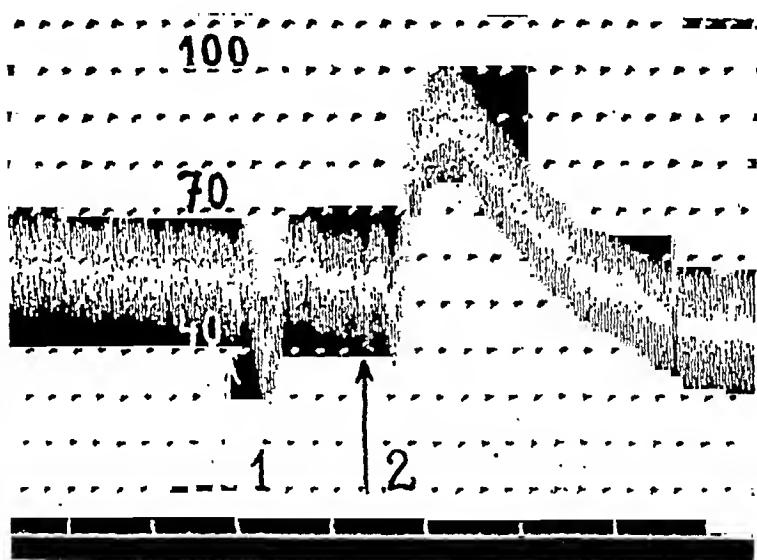


FIG. 4.—1, One unit of hypertensin incubated with pepsin at pH2. 2, The same with boiled pepsin solution. Alcoholic extracts injected to a chloralosed dog.

membrane was observed in chloralosed cats. In small doses (1 unit in 1000 cc. Ringer solution) it increased the height of contraction and the tonus of isolated rat or guinea pig uterus (which are inhibited by epinephrin), it stimulated contraction of rabbit uterus (as does epinephrin), it increased the tone of rat's gut (as does acetylcholine) and this action was not inhibited by atropine (Ludueña, unpublished results).

**E. Hypertensinase.** When blood serum is incubated with renin, the amount of hypertensin increases rapidly, then decreases and finally disappears.<sup>3a,b,24</sup> This disappearance is produced by serum and also by renin if impure preparations are used.

If 1 unit of hypertensin is incubated with 2 cc. of dog's serum (total volume, 2.5 cc.) at 37° C., the activity disappears gradually.

The pressure increases caused by the corresponding extracts were as follows:

Time of incubation in minutes . . .	0	15	30	45	60	90
Pressure increases in mm. Hg . . .	45	30	15	12	8	5

The hypertensinase of serum can be destroyed by incubating at 37° C. during 15 minutes, after adjusting the pH to 3.9. Under these conditions renin and hypertensin precursor remain unaltered. Impure renin solutions are highly active in destroying hypertensin as are also extracts of liver and spleen. Hypertensinase is destroyed by heating and has a pH optimum between 7.5 and 8.5 (Fig. 1). It can be therefore considered as an enzyme. The action is not suppressed by anaërobiosis, cyanide, octyl alcohol, chloroform and thymol.

Some measurements of hypertensinase activity of serum before and 48 hours after nephrectomy were carried out in dogs.

Samples of serum (1 to 2 cc.) were incubated 1 hour at 37° C. with 1 unit of hypertensin and the alcoholic extracts injected to chloralosed dogs. The pressure increase was compared with that produced by 1 unit of hypertensin. The differences per cent were as follows:

Before nephrectomy . . .	-34	-47	-20	-10	-89	-46
After nephrectomy . . .	+21	+15	+25	+10	-19	+8

These results show a clear decrease in the hypertensinase activity of blood after nephrectomy.

There are several observations which indicate that normal kidney exerts some sort of protective action against pressure increases produced by renal ischemia.<sup>6a,b</sup> If ischemia is produced in one kidney, the blood pressure increase is smaller when the other kidney remains intact. In many cases the pressure even returns to normal levels. When the artery of one kidney is compressed, it has often been observed that hypertension is produced only after the normal kidney is extirpated.<sup>6a,7,19</sup>

Some promising results have already been obtained in the treatment of experimental hypertension. Renin solutions when injected in large amounts sometimes produce a decrease in blood pressure. This effect can be interpreted as due to the fact that these solutions contain an antipressor substance. It has indeed been found that suitable kidney extracts can produce either a neutralization of the effect of renin,<sup>12</sup> or a decrease in pressure in hypertensive dogs.<sup>25</sup> Similar results on the hypertensive dog have been obtained in this laboratory, but the value of these experiments cannot yet be estimated. The antigenic properties of renin offer still another possibility and a beginning in this direction has been made by Johnson and Wakerlin,<sup>18</sup> who found that if a rabbit is repeatedly injected

with dog's renin, antibodies are formed so that the serum is capable of neutralizing the pressor effect of renin in the dog.

The better understanding of the mechanism of renal hypertension may give some indications as to the treatment of this disease. This should aim at: 1, suppressing or diminishing the secretion of renin by the kidney; 2, inhibiting the reaction of renin with blood globulin; 3, diminishing the amount of hypertensin precursor; 4, inhibiting the action of hypertensin by increasing the amount or the activity of hypertensinase or some other neutralizing agent.

**Summary.** The ischemic kidney secretes renin. This substance is an enzyme which acts on a blood globulin ("hypertensin precursor") and gives rise to a substance ("hypertensin") which has a direct vasoconstrictor action. Another enzyme "hypertensinase," which destroys hypertensin, is present in blood and tissues.

Hypertensin has been found in the blood of ischemic kidneys and can also be prepared *in vitro* by incubating renin with blood globulins. Some chemical and pharmacologic properties of hypertensin have been studied.

Methods are described for the estimation of renin, hypertensin precursor and hypertensinase in blood.

After injection of renin into chloralosed dogs, the hypertensin precursor decreases and even disappears from the blood. After nephrectomy, the hypertensin precursor increases and hypertensinase decreases.

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## CLINICAL EXPERIENCE WITH SULFAMETHYLTHIAZOLE.\*†

[2 (PARA-AMINO-BENZENE-SULFAMIDO) 4-METHYLTHIAZOLE.]

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WE have previously submitted a preliminary report<sup>1</sup> on the use of sulfamethylthiazole for several patients, one of whom recovered from septicemia, the etiologic agent of which was *Staphylococcus aureus*. Subsequently, there has appeared a brief clinical report on the use of this drug by Carroll and associates.<sup>4</sup> The thiazole derivatives of sulfanilamide, 2-sulfamidomethylthiazole, 2-sulfamido-4-methylthiazole and 2 sulfamido-4-phenylthiazole, have also been the subject of a preliminary report of the Council on Pharmacology and Chemistry of the American Medical Association and of a recent editorial in the journal of that Association.<sup>7</sup> We believe that the subject of sulfamethylthiazole is of sufficient importance to warrant a statement of our clinical experience with this drug to date.

The compound, sulfanilamide, has thus far formed the basis for a related group of therapeutically active substances. Efforts to produce a drug with greater therapeutic effect and with less toxicity have led to the production of many compounds only a few of which have been adaptable for clinical purposes. Of the various sulfonamide drugs in use at present, neoprontosil seems to possess less toxicity than sulfanilamide, but its therapeutic effect on the *Strep. hemolyticus* also appears to be somewhat less. Sulfapyridine is effective against the *Strep. hemolyticus* but has proved to be of particular value in the treatment of infections due to the *Dipl. pneumoniae*. In addition, sulfapyridine to date, when administered orally or intravenously as the sodium salt of sulfapyridine, in amounts sufficient to produce a high concentration of the drug in the blood, has thus far appeared to be the most useful drug in the treatment

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of infections due to the *Staph. aureus*. However, the use of sulfapyridine has been attended frequently by certain troublesome and dangerous manifestations of toxicity. These manifestations have included all of the toxic effects of sulfanilamide plus an increased tendency toward the occurrence of gastro-intestinal upsets such as nausea and vomiting. These latter effects although possibly due to some local irritative action may also be central in origin, for they are experienced by patients receiving only the sodium salt of sulfapyridine by the intravenous route. Renal complications due to the precipitation of acetylsulfapyridine crystals in the tubules and pelvis of the kidney are also known to occur. The subject of these latter changes has recently been reviewed by Plummer and McLellan<sup>15</sup> who stated that they may vary from simple calculous ureteritis and pyelitis that produces hematuria to severe pyelonephritis that results in renal insufficiency and azotemia. Experience has shown that any of these complications may make the problem of sulfamido therapy a difficult one at times.

In a search for some other compound which might afford a solution to some of these problems, we have previously used sulfanilyl-dimethyl-sulfanilamide (di-septal, ulinon) and have reported on our experience<sup>9</sup> with it and on our discarding of it.

Certainly any new compound which may be presented on a basis of experimental study that indicates lessened toxicity and increased therapeutic efficiency over other available compounds against the *Staph. aureus* warrants a thorough clinical trial. It must be borne in mind, however, that past experience has indicated a definite difference between toxic effects as exemplified by animal experiments on the one hand and the response of human beings on the other.

In August, 1939, Fosbinder and Walter<sup>8</sup> found that heterocyclic amino compounds other than 2-aminopyridine might be coupled with the sulfanilyl radical without great change in physiologic activity. In summary, they stated that the thiazole compounds appeared to possess activity comparable to that of sulfanilamide and sulfapyridine.

Following this, there appeared in November, 1939, simultaneous reports by van Dyke, McKee, and associates,<sup>6,14</sup> and by Cooper<sup>5</sup> and associates on animal experiments with the thiazole compounds. The former group working only with sulfathiazole reported favorably on its use. Cooper and his associates found that sulfathiazole and sulfamethylthiazole were equal to sulfanilamide in therapeutic effect but were slightly inferior to sulfapyridine when orally administered in the treatment of streptococcal and Type II pneumococcal infections in mice. They did not take into consideration, as Long and Bliss<sup>12</sup> have pointed out, that an adequate concentration of the thiazole compounds in the blood may not have been present due to the rapid absorption and elimination of these drugs on oral adminis-

tration. Rake and associates<sup>16</sup> have reported that the chronic toxicity of sulfathiazole for mice was greater than that of sulfapyridine but that the latter compound was more toxic in rats and monkeys.

In December, 1939, Barlow and Homburger<sup>2a</sup> reported on studies of sulfathiazole, sulfamethylthiazole, and sulfaphenylthiazole. They concluded from the treatment of experimental infections with *Staph. aureus* in mice that sulfathiazole and sulfamethylthiazole were superior to sulfapyridine in their therapeutic actions on these infections. They found that in a significant number of mice treated with the thiazole compounds, the kidneys, prostate gland, liver and spleen were essentially normal save for a few scars from healed abscesses. Later<sup>2b</sup> they demonstrated in experimental infections in mice that the chemotherapeutic effects of sulfathiazole and sulfamethylthiazole were superior to those of sulfanilamide and were equal to those of sulfapyridine in infections due to *Beta* hemolytic streptococci and due to pneumococci, Types I, II, and III. From experiments for tolerance of single doses and also for chronic tolerance of the sodium compounds of sulfamethylthiazole and sulfapyridine, they found that the latter preparation was more toxic than sulfamethylthiazole. They concluded that on the basis of this superior margin of safety, sulfathiazole and particularly sulfamethylthiazole appeared favorable when compared with sulfanilamide and sulfapyridine.

Lawrence<sup>10</sup> reported, following experiments on broth cultures, that the three thiazole compounds, sulfathiazole, sulfamethylthiazole, and sulfaphenylthiazole, were superior to sulfanilamide and sulfapyridine in their bacteriostatic effects on pneumococci, Types I, II and III, *Beta* hemolytic streptococci, gonococci and the *Staph. aureus*.

Long and Bliss<sup>12</sup> have concluded that sulfathiazole is as effective a bacteriostatic agent as sulfapyridine in broth cultures of certain strains of Lancefield's Groups A, D, and G, *Beta* hemolytic streptococci, *Escherichia coli*, *Staph. aureus*, pneumococci, Types I and II, and *Proteus vulgaris*. Sulfathiazole was slightly less effective than sulfapyridine in controlling experimental pneumococcal infections in mice, probably due to the more rapid absorption and excretion of the former drug.

Long, Haviland, and co-workers<sup>13</sup> recently reported, after experimental studies with sodium salts in mice, that sulfathiazole had a lower toxicity than sulfapyridine, but that addition of the methyl group increased its toxicity 50%, and that the latter preparation was therefore more toxic than sulfathiazole or sulfapyridine.

On the basis of these early reports, particularly of Barlow and Homburger,<sup>2a, b</sup> which indicated that sulfamethylthiazole was particularly effective against staphylococcal infections and possessed a low toxicity, we began the use of this drug orally in certain selected cases at The Mayo Clinic. We attempted primarily to treat patients

who had infections produced by staphylococci and pneumococci, but we also used the drug against infections caused by organisms other than staphylococci and pneumococci or against infections of unknown etiology in an endeavor to gain information regarding its action. We realize, of course, that it is not possible to draw entirely accurate conclusions from the study of a small group of cases such as is presented herein; nevertheless, we believe that the study will allow certain tentative and some definite conclusions to be made regarding the therapeutic action of the drug and its toxicity.

We are reporting at this time on the use of sulfamethylthiazole in the treatment of 106 patients at The Mayo Clinic. For purposes of simplification, we have roughly classified the infections encountered as follows: pneumonia, 30 cases; septicemia, 7 cases; subacute bacterial endocarditis, 5 cases; pelvic infections, 5 cases; infections of bone, 4 cases; cutaneous infections, 25 cases; infections of the ear, nose and throat, 13 cases; urinary infections, 3 cases,\* and miscellaneous, 14 cases. The organisms identified in these various cases were: *Diplococcus pneumoniae* in 7, *Strep. hemolyticus* in 7, *Staph. aureus* in 31, *Strep. viridans* in 6, *Strep. anaerobicus* in 1, *Escherichia coli* in 1, *Strep. faecalis* in 1, and *Klebsiella pneumoniae* in 1.

In the treatment of all of these patients, the doses of sulfamethylthiazole employed in general were similar to those which we have given when using other sulfamido drugs. The doses averaged from 4 to 6 gm. daily for adults with moderate infections, to as high as 13 gm. daily for adults with septicemia and subacute bacterial endocarditis. The general policy toward adults with severe infections such as septicemia was to give 4 to 5 gm. as an initial dose and to follow this by 1 to 1.5 gm. every 4 hours as a maintenance dose. In the event that a satisfactory result was not obtained or the concentration of the drug in the blood was low, these doses were increased to as much as 2 gm. every 4 hours for periods of 4 and 5 days. For adults with infections of moderate degree, the general procedure was to give 4 to 6 gm. daily in 5 or 6 divided doses. In several of these cases, when it seemed impossible to obtain a satisfactory concentration of the drug in the blood by oral therapy, the sodium salt of sulfamethylthiazole was given intravenously.

Sodium sulfamethylthiazole was obtained by adding sodium hydroxide to sulfamethylthiazole in equal molecular proportions; the molecular weight of sulfamethylthiazole is 269 and that of sodium hydroxide is 40. A 10% solution of sodium sulfamethylthiazole in distilled water was then prepared, and the pH of the solution was brought to approximately 10.4 by adding 3.7 cc. of normal sodium hydroxide. As with a solution of the sodium salt of sulfapyridine, this marked alkalinity made it necessary to avoid injection of any material into subcutaneous tissue. Approximately 1.5 gm. or 30 cc.

\* This does not include patients treated with sulfamethylthiazole in the Section on Urology.



of a 10% solution of sodium sulfamethylthiazole (not more than 50 mg. per kilogram of body weight) was given slowly intravenously as a single dose and the dose was repeated in 3 to 4 hours if necessary. This 10% solution of sodium sulfamethylthiazole in distilled water was also given in amounts up to 2.5 gm. in 1 liter of 5% solution of glucose. We noted no untoward effects from the use of this form of treatment and found that we were able to produce the desired concentrations of the drug in the blood. When an attempt was made to give 5 gm. of the 10% solution of sodium sulfamethylthiazole in 1000 cc. of a 5% solution of glucose, crystallization of the solution occurred within 12 hours and was not affected by heating.

The concentrations of the drug in the blood were estimated by A. E. Osterberg according to the method for sulfanilamide by Bratton and Marshall,<sup>3</sup> but a standard prepared from sulfamethylthiazole instead of from sulfanilamide was employed. Observations on these concentrations indicated that the values for sulfamethylthiazole in the blood were inclined to follow those levels of sulfapyridine obtained when the latter drug was given but were slightly lower. Frequently it seemed impossible to maintain adequate concentrations of the drug even when increased amounts were given orally. On average oral doses of 4 to 6 gm. daily, concentrations of the free drug in the blood varied from less than 1 mg. to 9 mg. per 100 cc. and the majority of values ranged between 3 and 4 mg. per 100 cc. The highest concentrations encountered ranged in a few instances from 10.2 to 15.4 mg. per 100 cc. in patients who received 11 to 13 gm. of the drug daily. Of striking interest was the fact that the values for the conjugated drug in the blood were quite low at all times and that the concentration of the free drug closely approximated the total concentration in each instance. It seemed possible that, whereas total values for sulfapyridine might run higher on comparative drug doses, the free values of sulfamethylthiazole more closely approximated those of free sulfapyridine. Illustrated representative values for comparative total and free concentrations of sulfamethylthiazole in mg. per 100 cc. of blood are as follows: free 1.0 and total 2.3; free 2.2 and total 2.8; free 7.4 and total 10.4. The pattern of high concentrations of the drug in the urine as seen with sulfanilamide and sulfapyridine was also followed. On average doses of 4 to 6 gm. of sulfamethylthiazole daily, representative concentrations of the drug in mg. per 100 cc. of urine were as follows: free 130 and total 215; free 195 and total 195; free 67.5 and total 185.

With the exception of the extremely significant and important complication, lower motor neurone involvement, which occurred in 3 cases, we were impressed by the general lack of common toxic manifestations produced by sulfamethylthiazole. Anorexia, nausea, or mild emesis were the toxic symptoms most frequently encountered, but their occurrence was much less than we have noted with the use of sulfapyridine. Of the 101 patients treated, there were 20 with

anorexia, nausea, or emesis. Of these patients 15 had mild symptoms, 2 had symptoms of a moderate degree and 3 had severe symptoms. Of these 20 patients with anorexia, nausea, or emesis, there were 2 who had had previous similar symptoms to the point of intolerance with the use of sulfapyridine. There were also 7 patients in this group who had marked nausea and emesis when sulfapyridine was used previously but who had no similar symptoms when they were subsequently given sulfamethylthiazole. In only 3 instances were these symptoms of sufficient degree to necessitate discontinuing treatment.

The toxic effect of sulfamethylthiazole which occurred next in frequency was a cutaneous eruption which 9 patients experienced. All of these lesions were of a maculopapular urticarial type and were accompanied by mild pruritus and, at times, by a fever of 99 to 100° F. (37.2 to 37.7° C.). The eruption tended to occur mostly on the upper part of the trunk but it also involved the neck, abdomen and extremities. In each instance it appeared between the seventh and tenth days of treatment and disappeared promptly within 20 to 30 hours after administration of the drug was discontinued.

In none of the patients treated was there any evidence of a change in the number of leukocytes suggestive of leukopenia or agranulocytopenia, and only 1 patient had a significant decrease in the number of erythrocytes. This patient had chronic uveitis and had received a total of 45 gm. of sulfamethylthiazole. The number of erythrocytes per cubic millimeter of blood progressively decreased from 4,780,000 to 3,470,000 during the sixth to ninth days of treatment and then remained stationary after administration of the drug was discontinued. There seemed to be no tendency for the drug to cause a decrease in the carbon dioxide-combining power of the blood. There was no evidence of pyelonephritis or involvement of the urinary tract of any of these patients save one who received sodium sulfamethylthiazole intravenously and who had a concentration of 20.2 mg. of the drug per 100 cc. of blood. This patient had *Staph. aureus* septicemia, and the case (Case 4) is considered in detail later in this discourse. Cyanosis was questionably discernible in only 3 cases, and in none was there found any significant amount of methemoglobin or sulfmethemoglobin by spectroscopic methods.

The most important complication encountered was lower motor neurone involvement, a condition which offers a real contraindication to indiscriminate use of sulfamethylthiazole. We believe that this condition is more accurately described by the term "lower motor neurone involvement" giving rise to muscle weakness than by the term "peripheral neuritis," as the disturbances present were not of a sensory nature but were of the nature of a pure motor weakness. The lesions which occurred showed an absence of muscle tenderness and presented no loss of pain, touch or temperature sensation. The occurrence of this complication served as a reminder of previous

experiences with sulfanilyl dimethyl sulfanilamide. Appearing as it did, after an experience with sulfamethylthiazole used in varying doses for approximately 100 patients, it again illustrated the fallacy of a general interpretation of the results of experiments on toxicity of the drug for animals when these results are applied to man. It is of interest in this regard that, in general, experiments on animals showed the toxicity of this drug to be quite low.

Long's<sup>11</sup> studies have recently indicated that the addition of phenyl or methyl groups to the thiazole compounds might increase their toxicity. No physiologic explanation for the occurrence of this complication with certain sulfamido compounds has yet been found. One of these patients had serious, chronic systemic disease complicated by pneumonia, empyema and repeated hemorrhage. There had previously been used 13.5 gm. of sulfanilamide and 13 gm. of sulfapyridine. The patient was intolerant to these drugs, and subsequently 17 gm. of sulfamethylthiazole were given in a 3-day period, 43.5 gm. in an 8-day period 1 month later, and 19 gm. in a 4-day period several days later. We judged the drug to have been of marked value to this patient. Lower motor neurone involvement as evidenced by bilateral foot-drop was noted some time after the administration of sulfamethylthiazole had been discontinued. The rôle of sulfamethylthiazole is not definite here and the weakened general condition of this patient may have been a definite factor in the production of this complication. The other 2 patients who experienced this condition were ambulant. In 1 instance, 38 gm. of the drug had been given in a period of 7 days, and in the other, 71 gm. had been given in 13 days. Both of these patients had chronic disease that had been resistant to previous treatment and the drug appeared to be of definite benefit. In each patient, foot-drop appeared bilaterally between 1 and 2 weeks after administration of the drug was stopped. In addition, 1 patient had mild weakness of the forefinger and thumb of both hands. Pain in the calves of the legs immediately preceded the onset of foot-drop. All of these patients have made definite and marked improvement (graded 75%) with regard to the lower motor neurone involvement. Vitamin B<sub>1</sub> has been given to all.

Of the total of 106 patients, there were 30 with pneumonia, and of these, 27 had bronchopneumonia and 3 had lobar pneumonia (Table 1). There were no deaths among the 27 who had bronchopneumonia, and the results were considered good in 13 cases and poor in 14. Of the 13 patients who obtained good results, the temperature became normal on the first day after treatment in 2, and on the fourth day in 2. The rapidity of response to therapy in these 4 cases was such as to suggest the presence of lobar pneumonia, but pneumococci were not found in the sputum. In 12 of these 13 cases in which the results were graded good, the temperature became normal in 8 days, and in the other, the temperature was

normal on the tenth day. The results were recorded as poor in 14 cases because fever persisted for more than 10 days, even though some significant lowering of fever and general improvement occurred in some after use of the drug. In these 14 cases, empyema occurred in 2, pleural effusion in 2 and serious preëxisting systemic complications were present in 3. Excellent and striking results were obtained by the 3 patients who had lobar pneumonia (Type I pneumococcus), and in each of these instances, the temperature promptly fell to

TABLE 1.—SUMMARY OF EXPERIENCE WITH 30 CASES OF PNEUMONIA, IN WHICH SULFAMETHYLTHIAZOLE WAS EMPLOYED.

	Bronchopneumonia.		Lobar pneumonia.	
No. of patients . . . . .	27: 14 males, 13 females		3: 2 males, 1 female	
Range of ages, years . . . . .	2 to 78		2 to 7	
Average age, years . . . . .	42.6		4.0	
Extent of pulmonary involvement . . . . .	1 lobe, 14 cases; 2 lobes, 13 cases		1 lobe, 4 cases	
Postoperative complication . . . . .	8 cases		None	
Range of treatment, days . . . . .	3 to 21		7 to 8	
Average dur. of treatment, days . . . . .	7		7.7	
Average dose of sulfamethylthiazole per course of treatment, gm. . . . .	30.2		22.1	
Average daily dose of sulfamethylthiazole, gm. . . . .	4.0		2.8	
Supplementary intravenous use of sodium salt . . . . .	2 cases		None	
No. of days of treatment that preceded normal temperature . . . . .	Days	Cases	Days	Cases
	1	2	1	3
	2	2		
	4	2		
	5	1		
	6	2		
	8	3		
	10	1		
	10+	14		
Results . . . . .	Good, 13 cases (48.1%) Poor, 14 cases (51.8%)		Good, 3 cases (100%) None	
Complication of empyema . . . . .	2 cases		None	
Organisms cultured from sputum . . . . .	<i>Strep. hemolyticus</i> , 1 case <i>Strep. viridans</i> , 1 case <i>Staph. aureus</i> , 1 case <i>Diplococcus pneumoniae</i> , Type VI, 1 case <i>Diplococcus pneumoniae</i> , Type XVI, 1 case <i>Diplococcus pneumoniae</i> , Group E, 1 case Unidentified, 12 cases		<i>Diplococcus pneumoniae</i> , Type I, 3 cases	
Reactions from sulfamethylthiazole . . . . .	Mild anorexia, nausea and emesis, 2 cases Marked anorexia, nausea and emesis, 1 case Exanthem, 3 cases Lower motor neurone involvement, 1 case None, 20 cases (74%)		None, 3 (100%)	
Previous reaction to sulfapyridine and no reaction to sulfamethylthiazole . . . . .	3 cases		None	
Range of concentration of sulfamethylthiazole in the blood, mg. per 100 cc. . . . .	1 to 12.2		1 to 4.2	
Average concentration of sulfamethylthiazole in the blood, mg. per 100 cc. . . . .	3.2		1.3	

normal within a period of 24 hours. Temperature charts of these 3 patients are shown in Figure 1a, b, and c. In treating patients who had pneumonia, the general tendency was to give two successive doses of sulfamethylthiazole of 2 gm. each at intervals of 4 hours to adults and then to continue with 1 gm. every 4 hours. More detailed data regarding these patients may be obtained from Table 1.

A group of 6 patients with *Staph. aureus* septicemia were treated with sulfamethylthiazole. Of these, 3 were men and 3 were women,

and their ages ranged from 23 to 62 years. Sulfapyridine had been administered to 2 of these patients preceding the use of sulfamethylthiazole and its administration was discontinued because of severe nausea and emesis. Sulfamethylthiazole was well tolerated by these 2 patients. The initial blood culture in all but one of these cases showed 100 or more colonies of organisms per cubic centimeter of blood. Four of these patients died and 2 recovered. All of the cases in which death occurred are of sufficient interest to warrant being briefly reported.

### 2/4 - Type I Pneumonia

Chest x-ray: 2/3 - Consolidated left lower  
2/11 - Negative

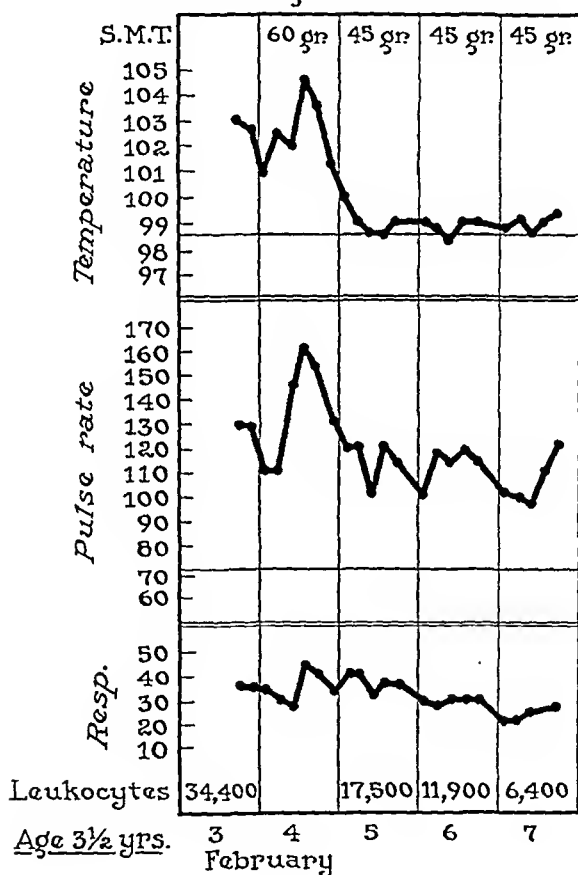


FIG. 1a.

**Case Reports.** CASE 1.—A man aged 58 had a septic fever to 104° F. (40° C.) 3 days after a transurethral prostatic resection and had been treated with 16 gm. of sulfanilamide over a period of 6 days because of infection in the urinary tract. Chills and fever had been present for 13 days, and a culture showed 200 colonies of organisms per cubic centimeter of blood 3 days before treatment with sulfamethylthiazole was started. This patient was given 23 gm. of the drug orally in 3 days, and at the end of this time, a culture

showed a reduction to 80 colonies of organisms per cubic centimeter of blood. The concentration of the drug in the blood reached 6.6 mg. per 100 cc. At this time, a cerebrovascular lesion developed with a left hemiplegia and chemotherapy was discontinued. Postmortem examination showed infarcts in the brain and ulcerative endocarditis.

CASE 2.—A man, aged forty-eight,\* had been acutely ill for a week. A culture gave evidence of "innumerable organisms" per cubic centimeter of

### 2/5 - Type I Pneumonia

Chest x-ray: 12/28 - Pneumonia right upper and lower

Chest x-ray: 2/3 - Consolidated right middle  
2/11 - Negative

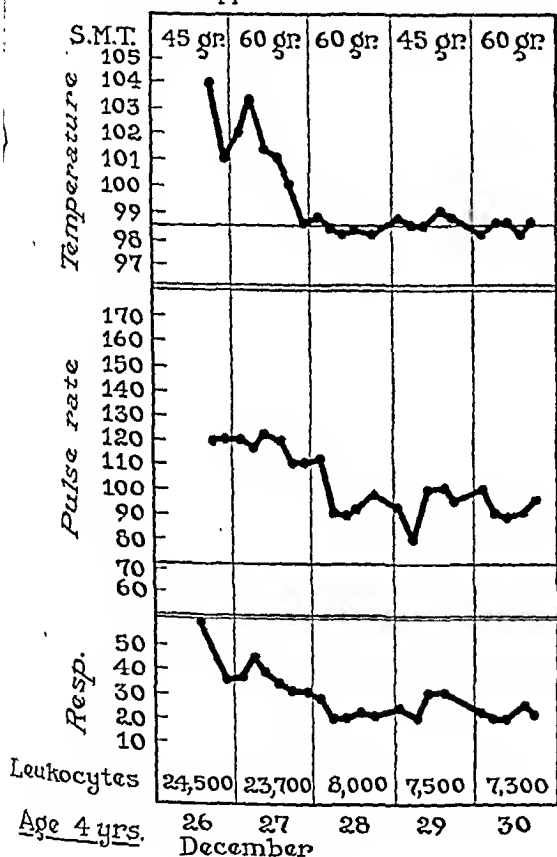


FIG. 1b.

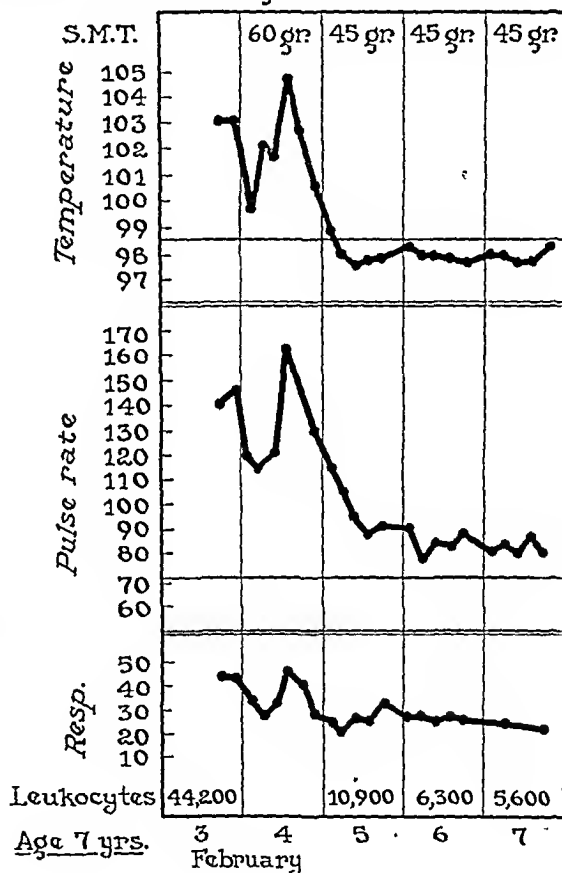


FIG. 1c.

FIG. 1a, b and c.—Temperature, pulse and respiration in 3 cases of lobar pneumonia, treated with sulfamethylthiazole.

blood for 2 days preceding sulfamethylthiazole therapy. Neoprontosil and sulfapyridine had been given previously. This patient received 54.5 gm. of sulfamethylthiazole orally in 6 days without improvement. No determinations of concentrations of the drug in the blood were made. Postmortem examination showed metastatic miliary abscesses of the lungs and kidneys and acute splenitis.

\* This patient was seen in consultation through the courtesy of Drs. Lepak and Scott of St. Paul.

CASE 3.—A woman, aged 62, was treated 3 days after the onset of fever and chills and 1 day after a culture with 300 organisms per cubic centimeter of blood was obtained. She was given 88.5 gm. of sulfamethylthiazole in 8 days without benefit. A concentration of 10.4 mg. of the drug per 100 cc. of blood was obtained. Postmortem examination revealed ulcerative endocarditis with abscesses of the lungs, liver and kidneys, and a terminal bilateral bronchopneumonia.

CASE 4.—This case was of particular interest. This patient, a woman of 45, was in a state of severe inanition as the result of chronic tuberculous endometritis and salpingitis. She had in addition, a widespread exfoliating cutaneous lesion suggestive of pemphigus foliaceus. Anorexia and vomiting had existed for some time, and it proved impossible after trial of sulfamethylthiazole orally for 3 days to obtain a concentration of the drug in the blood greater than 2.3 mg. per 100 cc. Subsequently, the drug was administered solely by intravenous methods for a period of 8 days and during this time the patient was sustained entirely by intravenous fluids. The concentration of the free drug in the blood was maintained between 12 and 20 mg. per 100 cc. At the later point there was a temporary suppression of urine which disappeared in 24 hours when the concentration in the blood was lowered to 12 mg. per 100 cc. No significant changes occurred in the number of erythrocytes or leukocytes. Definite clinical improvement occurred and the temperature became approximately normal. The number of colonies of organisms per cubic centimeter of blood progressively decreased as follows: 100, 50, 50, 6, 4, and 2. The last culture was obtained in the final 24-hour period of life. Death appeared due to inanition rather than to sepsis. Of special interest is the fact that, at necropsy, no abscesses were found in the liver, kidneys or lungs. There was a considerable accumulation of acetyl-sulfamethylthiazole crystals in the pelvis of each kidney, but these accumulations had not seemed to interfere with the excretion of urine.

All patients who have staphylococcal septicemia present a grave aspect, and we should feel that the prognosis under similar conditions to those which prevailed in the aforementioned cases seems hopeless.

Of the 2 cases in which recovery occurred, 1 has been previously reported. The other was that of a man who had pneumonia and who on two successive occasions was found to have 30 and 25 colonies of organisms, respectively, per cubic centimeter of blood. This patient made a rapid recovery following oral administration of the drug.

One patient, a man of 59, had a *Klebsiella pneumoniae* septicemia. He had been acutely ill for many months with this condition and had failed to respond to intensive treatment with sulfanilamide and sulfapyridine. He was treated with large doses of sulfamethylthiazole (78 gm. in 8 days) just preceding death, but the course of the disease remained unaltered.

Five patients with subacute bacterial endocarditis were treated with sulfamethylthiazole; the total amounts varied from 38 to 214 gm. over periods of 6 to 26 days. In each case there occurred some decrease in the number of colonies of *Strep. viridans* per cubic centimeter of blood, and in 3, temporarily, the culture resulted in no growth. In spite of some mild temporary improvement in symptoms, the disease was fundamentally unaffected by treatment which we considered a failure in each instance.

In 5 cases of pelvic inflammatory disease not of gonococcal origin sulfamethylthiazole was used in treatment. In 3 of these cases, this lesion was secondary to carcinoma of the cervix. In 1 instance the result was good, in another fair and in another poor. In another case in which carcinoma of the rectum and an associated pelvic abscess were present anaerobic streptococci were cultured from the abscess, and the disease was treated in its terminal stages but death occurred. In all of the other cases, the causative organism was not identified. The fifth case was one in which an acute inflammatory pelvic lesion was present which responded promptly to sulfamethylthiazole.

Four patients with osteomyelitis were treated with sulfamethylthiazole. One of these patients had multiple sinuses from a chronic paravertebral abscess and his condition was unimproved after he received 36 gm. of the drug in 9 days. In 2 other cases, the *Staph. aureus* was found in pus from draining abscesses. In 1 of these cases, the temperature became normal on the fifth day of treatment, and in the other, on the twelfth day of treatment; in the latter case, one aspiration was made from the abscess. In the fourth case, a recurrent osteomyelitis of the right femur was present from which the *Staph. albus* had previously been recovered. The temperature became normal and recovery occurred after he had received 25 gm. of sulfamethylthiazole.

There were 25 patients with various types of infections that involved the skin and subcutaneous tissues. Significant data concerning these patients are grouped in Table 2.

TABLE 2.—SULFAMETHYLTHIAZOLE THERAPY IN CUTANEOUS INFECTIONS.

	No. of patients.	Organism isolated from lesion.	Results.	Average total dose of drug, gm.	Average no. of days of medication.	Average daily dose of drug, gm.
Dermatitis with infection . . .	3	<i>Staph. aureus</i> in 3	Good	31.3	7.3	4.2
Pemphigus . . .	1	<i>Staph. aureus</i>	Fair*	48.0	8.0	6.0
Furunculosis or carbuncle . . .	4	<i>Staph. aureus</i> in 2	Good	28.1	4.7	6.0
Cellulitis . . .	5	<i>Staph. aureus</i> in 2 <i>Strep. hemolyt.</i> in 1	Good	31.2	5.8	5.3
Abscess . . .	5	<i>Staph. aureus</i> in 5	Good (3) Fair (2)	43.3	9.0	4.8
Wound infection . .	7	<i>Staph. aureus</i> in 3	Good (3) Fair (3)	27.6	6.2	4.4

\* Temporary.

There were 13 patients with various infections that involved the ear, nose, and throat. These lesions were roughly grouped as follows: sinusitis (postoperative), 2 cases; otitis media, 4; mastoiditis (post-



operative), 2; vestibulitis, 1; laryngitis, 1; pharyngitis with cervical adenitis, 2; and acute tonsillitis, 1 case. *Staph. aureus* was cultured from 3 of these lesions and *Strep. hæmolyticus* from 5. Although the results from treatment in general were judged to be good, we believe that it is impossible to draw any definite conclusions from a small series of cases of this type and we do not feel that a detailed analysis is of value.

TABLE 3.—MISCELLANEOUS CONDITIONS.

Condition.	Case.	Sex.	Age, yrs.	Sulfamethylthiazole.			Comment on result.
				Total dose, gm.	Total no. of days.	Av. daily dose, gm.	
Chancroid	1	M	35	40	10	4	Marked healing at time drug discontinued on dismissal.
	2	M	51	24	6	4	Marked healing at time drug discontinued on dismissal.
Lymphogranuloma inguinale	3	M	46	54	10	5.4	Marked improvement in rectal condition with relief of pain present for 14 months.
Trachoma	4	M	38	35	7	5	Ten-year history. Improvement in vision and in appearance of conjunctiva.
Bilateral uveitis	5	F	36	45	9	5	Two-year history. Previous failure of various types of therapy. On dismissal left eye improved 98% and right eye 75%.
Meningitis ( <i>Esch. coli</i> with brain abscess)	6	M	52	56	9	5.2	Three-month history with previous hemolytic streptococcal meningitis. Improved and negative spinal fluid culture.
Chronic ulcerative colitis	7	M	22	71	13	5.4	Improvement with decrease in number and consistency of stools to normal and absence of blood in stools.
Indeterminate fever	8	F	45	31	9	3.4	No benefit. Postmortem examination later revealed extensive thrombophlebitis.
Cholangitis; biliary cirrhosis	9	F	31	25	5	5	Previous failure of neoprontosil therapy. Striking result; patient afebrile and clinically improved in 24 hours.
Fracture dislocation, 5th cervical vertebra	10	F	18	73.5 39	12 6	6.1 6.5	Patient with partial Brown-Séquard syndrome seen 48 hours after accident. Paralysis of muscles of thoracic wall and of deglutition. Urinary retention. Unusual recovery without complication with use of drug as prophylactic.
Localized purulent bronchitis	11	M	43	47	7	6.7	Six weeks of illness with fever and cough. Bronchoscopy revealed localized purulent bronchitis. Temperature normal after 6 days of treatment.
Empyema	12	F	51	24.5	8	3	Three weeks of illness. Rib resection necessary. No benefit from the drug.
Postoperative pneumonectomy	13	M	44	80.5	11	7.3	<i>Strep. viridans</i> in chest fluid. Decline in temperature to 99° F. after 6 days of treatment.
Postoperative thoracotomy for cyst of lung	14	M	34	30	6	5	<i>Staph. aureus</i> in drainage. <i>Pneumonia</i> Type D in sputum. Decline in temperature to 99° F. in 4 days.

Three patients with infections of the urinary tract were treated and all improved. *Staph. aureus* was recovered from the urine of 1 patient and *Strep. faecalis* from the urine of another.

Fourteen patients have been listed in a miscellaneous classification which includes the conditions given briefly in Table 3.

**Comment.** One hundred and six patients with various types of infections have been treated with sulfamethylthiazole. The diseases for which treatment was given together with the number in each group have been roughly classified as follows: pneumonia, 30 cases; septicemia, 7; subacute bacterial endocarditis, 5; pelvic infections, 5; bone infections, 4; cutaneous infections, 25; infections of the ear, nose and throat, 13; urinary infections, 3; and miscellaneous types, 14 cases.

Sulfamethylthiazole was administered orally to the majority of patients in doses similar to those employed when we have used sulfanilamide and sulfapyridine, with the exception that larger doses were frequently used for and tolerated by the severely ill patients. The sodium salt of sulfamethylthiazole was used intravenously for 3 patients and it produced significant elevations of the concentration of the drug in the blood.

Sulfamethylthiazole, when used orally, produced concentrations of the free drug in the blood similar to but somewhat lower than those resulting from the use of sulfapyridine, and a minimal amount of conjugation occurred.

We realize that it is not possible to draw conclusions which may be entirely satisfying from a small series of 106 cases. We believe, however, that the results obtained to date justify confidence that the clinical, therapeutic effect of sulfamethylthiazole substantiated experimental predictions. Infections produced by the *Staph. aureus* and the *Diplococcus pneumoniae*, Type I, in particular seem to respond to treatment.

With the exception of the highly important and significant complication of lower motor neurone involvement in 3 cases and of cutaneous eruptions in 9, toxic effects seemed to be less than we have encountered with the use of sulfapyridine and also sulfanilamide. Significant nausea and emesis occurred infrequently. No serious disturbances resulted in the number of erythrocytes or leukocytes. No decline in the carbon dioxide-combining power of the blood was noted. No renal complications occurred save in 1 case in which acetylsulfamethylthiazole crystals formed in the renal pelvis.

**Summary.** Sulfamethylthiazole\* was used orally in 106 cases for various types of infections and the drug seemed to produce satisfactory results in a significant number. This was particularly true

\* Since this study was completed and recorded, sulfamethylthiazole has been withdrawn from clinical experimental use owing to occurrence of the complication of lower motor neurone involvement.

No evidence of infection was found after extensive studies. Cause of fever undetermined. On the chance that some infection might be present which would be amenable to treatment with the sulfonamide drugs, the patient was given sulfanilamide and later sulfapyridine. The depression of the expected temperature level by sulfapyridine is evident from the chart in Figure 1. That this effect was an antipyretic one is suggested by the fact that amidopyrine administered at a later date completely abolished the usual paroxysm of fever.

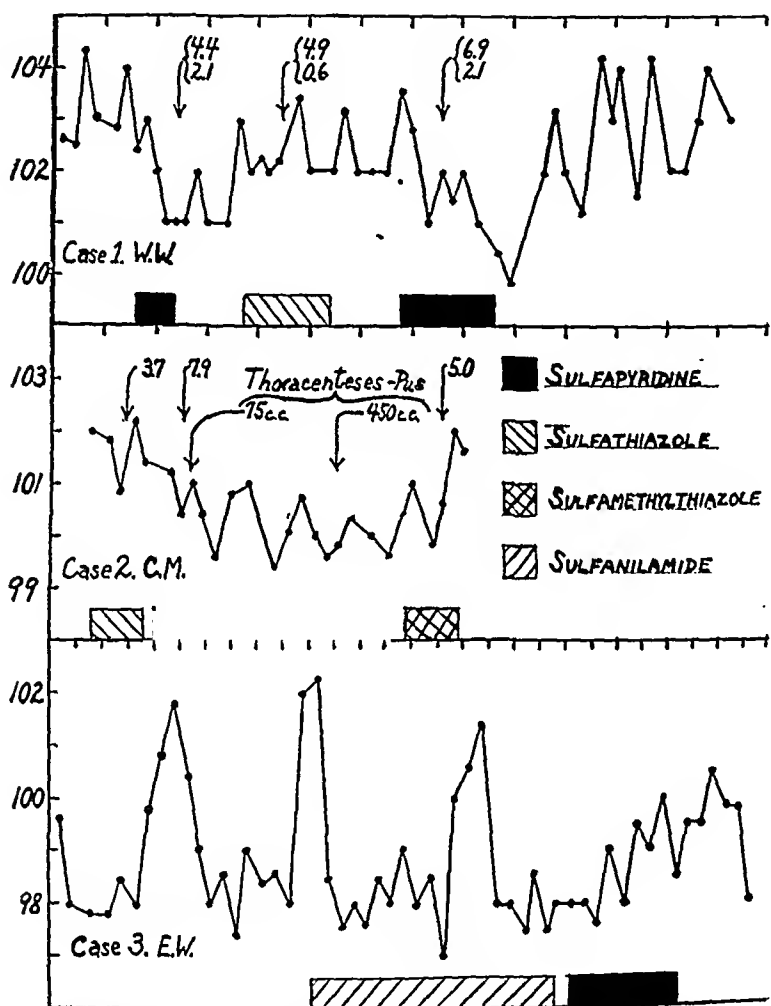


FIG. 1.—Effect of administration of sulfonamide compounds on temperature of patients in whom a direct chemotherapeutic effect may be reasonably well excluded. Numerals with arrows indicate blood concentration of the drugs. Where one figure is given it represents the level of free drug. Where two are given, the upper figure represents the concentration of free and the lower the concentration of combined drug.

**Experimental.** Experiments carried out in rabbits to test the effect of the sulfonamide compounds on the body temperature are reported herewith.

**Materials and Methods.** Adult female rabbits were used as experimental animals. White rabbits were used exclusively in later experiments, as it was found that results were more uniform with them. The drugs were administered after a preliminary period of several hours during which the normal rectal temperature for each rabbit was ascertained. For oral administration the drugs were suspended in 20 cc. water, warmed to body temperature and given by stomach tube. For intravenous injection the sodium salts of sulfapyridine and sulfathiazole were dissolved in warm distilled water and injected into the ear vein. In all experiments control animals were given equal amounts of water or saline by the same route of administration. Standard commercial typhoid vaccine was injected intravenously in some experiments in order to produce fever.

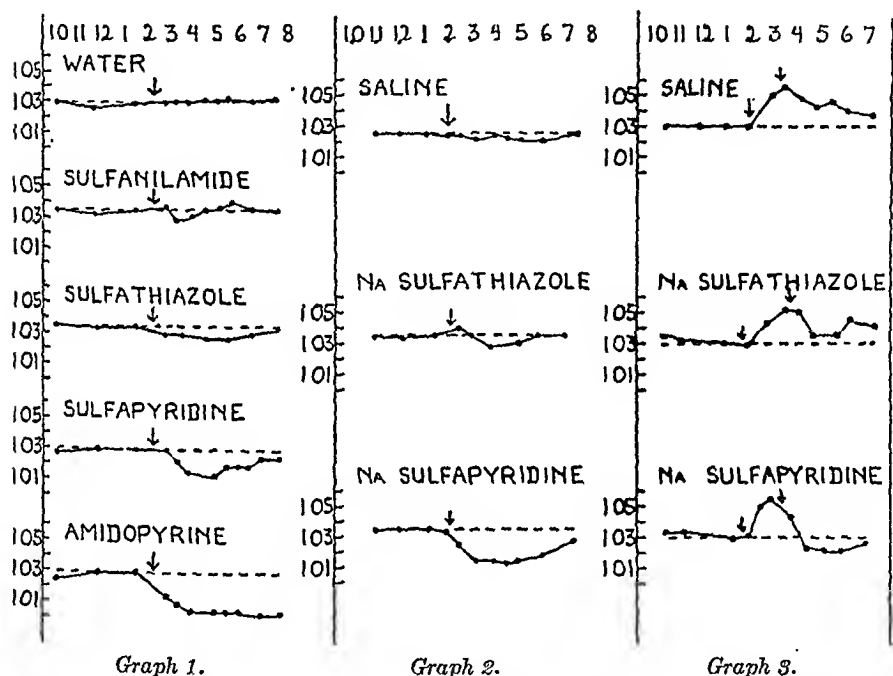


Fig. 2.—Graph 1: Effect of oral administration on normal temperatures of rabbits. One gram of test substance in 20 cc. of water given by stomach tube at arrow. Graph 2: Effect of intravenous administration on normal temperatures of rabbits. Five-tenths gram of test substance in 10 cc. distilled water injected at arrow. Graph 3: Effect of intravenous administration on temperatures of rabbits with pyrexia induced by typhoid vaccine. Five-tenths cubic centimeter of diluted typhoid vaccine injected at first arrow, 0.5 gm. of test substance in 10 cc. distilled water injected at second arrow.

**Results.** 1. *Effect of Oral Administration of Sulfanilamide, Sulfapyridine and Sulfathiazole on the Normal Temperature* (Fig. 2, Graph 1). Sulfanilamide and sulfathiazole had only a slight temperature-lowering action, but sulfapyridine was considerably more effective. Amidopyrine had a still greater effect. It should be noted that all drugs were given in equal amounts (1 gm.) in these experiments, whereas in clinical usage the dose of the sulfonamide compounds is usually many times as great as the dose of amido-

pyrine. Although the doses used were proportionately greater than those used in humans, the blood levels achieved were comparable, *e. g.*, 15 mg. per 100 cc. for sulfanilamide and 5 mg. per 100 cc. for sulfapyridine 3 hours after oral administration of 1 gm.

2. *Effect of Intravenous Administration of Sulfapyridine and Sulfathiazole on Normal Temperature.* The sodium salts of sulfapyridine and sulfathiazole dissolved in water were injected intravenously in doses of 0.1, 0.5 and 1 gm. With the smallest dose there was no appreciable effect on normal temperature. However, with either of the larger doses animals which received sulfapyridine showed a marked fall in temperature, while those receiving sulfathiazole showed little or no change in temperature. The alkalinity of these two salts is the same. Typical results are illustrated in Figure 2, Graph 2. The blood levels attained were somewhat higher than those usually encountered clinically, as shown in Table 1.

TABLE 1.—BLOOD LEVELS AND TEMPERATURE OF RABBITS FOLLOWING THE INTRAVENOUS ADMINISTRATION OF SODIUM SULFAPYRIDINE AND SODIUM SULFATHIAZOLE.

Rabbit.	Drugs.	Dose, gm.	Blood concentration (mg. per 100 cc.).				Temperature* (° F.) at		
			15 min. after injection.		3 hrs. after injection.		Start.	1½ hrs.	3 hrs.
			Free.	Com- bined.	Free.	Com- bined.			
1	Sodium sulfathiazole	0.5	17.1	3.1	2.1	0.8	103.0	102.7	102.8
2	Sodium sulfathiazole	0.5	25.5	2.2	6.3	0.5	103.0	103.2	102.9
3	Sodium sulfapyridine	0.5	19.2	8.6	1.9	9.3	102.6	101.5	102.5
4	Sodium sulfapyridine	0.5	11.6	2.8	1.2	6.4	103.0	102.2	102.0

\* The fall in temperature in this particular experiment was less striking than usual, probably because of the warm, humid day.

3. *Effect of Sulfonamide Compounds on the Fever Produced by Intravenous Administration of Typhoid Vaccine.* By the intravenous administration of typhoid vaccine, sharp temperature rises can be produced in rabbits; the rise usually begins about 30 minutes after injection and reaches its peak in an hour. When sulfanilamide, sulfathiazole and sulfapyridine were given orally before the vaccine injection the temperature responses of the animals were little different from those in the controls, except that there seemed to be a more rapid return to normal temperature in the rabbits which had received sulfapyridine. Similarly, when sodium sulfapyridine and sodium sulfathiazole were given intravenously before or at the same time as the vaccine there was no reduction in the height of fever attained by the treated animals, as compared with the controls, although animals which received sulfapyridine showed a more rapid return to normal temperature than the others. On the basis of these results a series of experiments were carried out in which sodium sulfapyridine and sodium sulfathiazole were given

intravenously when the peak of fever had been reached after the injection of typhoid vaccine. A typical experiment is illustrated in Figure 2, Graph 3. Animals receiving sodium sulfapyridine showed a rapid drop in temperature to the normal level or below, while those receiving sodium sulfathiazole underwent little or no drop in temperature, and did not reach normal any sooner than the controls.

4. *Effect of Acetyl Derivatives of Sulfonamide Compounds on Normal Temperature.* Since sulfapyridine and sulfathiazole differ in the extent to which they are acetylated in the blood of rabbits and humans, this might explain the difference between them in antipyretic action. Accordingly, the acetyl derivatives were tested for their effect on the normal temperatures of rabbits. Several experiments were performed using the oral route of administration and doses of 1 gm. It was possible to obtain satisfactory blood levels of both acetyl sulfanilamide and acetyl sulfapyridine by this method, but not of acetyl sulfathiazole, which is very insoluble. In these experiments neither acetyl sulfanilamide nor acetyl sulfapyridine affected the temperature significantly (blood concentrations were 5 to 10 mg. per 100 cc. of combined drug and less than 1 mg. per 100 cc. of free drug).

TABLE 2.—BLOOD LEVELS AND TEMPERATURES OF RABBITS FOLLOWING THE INTRAVENOUS ADMINISTRATION OF SODIUM SALTS OF THE ACETYL DERIVATIVES OF THE SULFONAMIDE DRUGS.

Rabbit No.	Drug.	Blood concentration, mg. per 100 cc.				Temperature.			
		Dose, gm.	Time of sample.	Frec.	Combined.	Start.	1½ hrs.	2½ hrs.	3½ hrs.
Experiment 1 at Room Temperature of 80° F.									
17	Sodium sulfapyridine	0.5	..	...	..	102.8	102.2	102.3	
4X	Sodium acetyl sulfapyridine	0.5	1½ hrs.	0.7	14.8	102.4	101.8	..	101.8
9	sulfapyridine	0.5	"	1.7	19.1	103.6	103.3	..	104.1
4	Sodium acetyl sulfathiazole	0.5	"	1.8	29.8	103.0	102.0	..	101.8
16	Sodium acetyl sulfanilamide	0.5	"	0.8	10.2	102.4	102.4	..	103.3
Experiment 2 at Cold Room Temperature of 45° F.									
4	Sodium sulfapyridine	0.5	2½ hrs.	21.2	22.4	103.0	100.6	101.0	101.5
17	Sodium acetyl sulfapyridine	0.5	"	1.0	15.2	103.7	101.3	101.0	102.0
16	sulfapyridine	0.4	"	0.9	5.4	103.0	101.8	102.6	102.8
4X	Sodium acetyl sulfathiazole	0.5	"	1.8	5.9	103.5	103.8	103.7	103.7
9	sulfathiazole	0.5	"	0.5	5.3	103.0	102.3	101.9	103.2
5	Sodium acetyl sulfanilamide	0.4	"	0.5	9.5	103.9	103.9	103.8	103.6

In order to get more satisfactory blood concentrations the drugs were dissolved in dilute sodium hydroxide, the excess alkali was neutralized by adding hydrochloric acid until a precipitate just began to appear, and these solutions were injected intravenously. Table 2 gives the results obtained in two experiments performed at different environmental temperatures. It is obvious that sodium acetyl sulfanilamide produced no change in the temperature, but it is more difficult to evaluate the effect of sodium acetyl sulfapyridine and sodium acetyl sulfathiazole. The latter drug lowered the temperatures of 2 of 3 rabbits. In Experiment 1 this effect per-

sisted, and in this rabbit the blood concentration was excessively high. Similarly, with sodium acetyl sulfapyridine, there was a lowering of the temperature of 3 of the 4 rabbits tested, but the effect only persisted in 2, and in these rabbits (No. 4X in Experiment 1 and No. 17 in Experiment 2) the blood levels were also high. If the temperature-lowering action of sulfapyridine is due to the formation of acetylated sulfapyridine in the body fluids, the intravenous injection of large amounts of sodium acetyl sulfapyridine should produce a much more extreme change in body temperature. Since this did not occur, we must conclude that acetyl sulfapyridine has some temperature lowering activity, but less than that of the free compound. The same seems to be true of sulfathiazole.

*Mechanism of Action.* Rises in body temperature may be caused by increased heat production, decreased heat loss, or both. Observation of the color and warmth of the rabbits' ears during these experiments suggested that some of the drugs acted to produce an increased loss of heat through the skin. Whenever the temperature was falling, as a result of the administration of amidopyrine, sodium salicylate, or sulfapyridine, the ears of the rabbits were warmer than those of rabbits whose temperatures were not falling. A few experiments were done to test this hypothesis. When rabbits were placed in an incubator room (temperature of 98° F. and high humidity) their temperatures rose to about 105° F., their ears became hot, and they panted and appeared prostrated. *Neither sulfapyridine nor amidopyrine had any effect in lowering the temperature under these circumstances.* When rabbits were placed in a cold room (temperature 45° to 50° F.) their body temperatures ranged between 102° and 103° F., their ears became cold, and the skin vessels were constricted. After the administration of sulfapyridine or amidopyrine there was a rapid fall in temperature, and the ears of the treated rabbits became warm.

**Discussion.** The measurement of changes in heat production was not feasible, hence it is impossible to go further than to state that the antipyretic action of sulfapyridine in rabbits is at least partially mediated through increased dissipation of heat from the skin. When that mechanism is thwarted, as in the incubator experiments, no fall in temperature occurs. Conversely, when the differential between body and air temperature is marked, as in the cold room experiments, a greater drop in temperature occurs.

These experiments indicate that sulfapyridine has a much more marked effect on the body temperature than sulfanilamide or sulfathiazole. This may be a point of some importance in the clinical evaluation of the effectiveness of these drugs, as in the comparison of sulfathiazole and sulfapyridine in the treatment of pneumonia.

**Summary.** 1. Clinical examples are presented in which it appeared that the fall in temperature following administration of sulfapyridine was due to an antipyretic action rather than to any effect on the infectious process.

2. In normal rabbits sulfapyridine caused significant lowering of the body temperature, while sulfanilamide and sulfathiazole caused only slight changes. Sodium sulfapyridine administered intravenously caused a prompt fall in body temperature, whereas, sodium sulfathiazole caused a slight drop.

3. Sodium sulfapyridine given intravenously at the height of fever induced by typhoid vaccine produced a rapid fall to normal or sub-normal temperature. Sodium sulfathiazole exerted a slight antipyretic action under these circumstances.

4. In normal rabbits acetyl sulfanilamide did not affect body temperature when given orally or intravenously as its sodium salt. Acetyl sulfapyridine and acetyl sulfathiazole did not affect the temperature when administered orally, but when given intravenously as their sodium salts produced a persistent drop in body temperature in certain rabbits with high blood concentrations. Sodium acetyl sulfapyridine was more effective than sodium acetyl sulfathiazole, but both drugs were less effective than the free compounds.

5. As far as could be ascertained, most of the antipyretic action of sulfapyridine was due to increased dissipation of heat from the skin.

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### INTUBATION STUDIES OF THE HUMAN SMALL INTESTINE.

#### XV. THE ABSORPTION AND EXPULSION OF GLUCOSE FROM THE STOMACH.\*

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THE work of several groups of investigators (London and Polowzowa;<sup>7</sup> Maddock, Trimble and Carey;<sup>8</sup> Macleod, Magee and

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Purves<sup>8</sup>) has given rise to the opinion that glucose is not absorbed from the stomach. A review of the literature, however, reveals that the majority of evidence (v. Anrep;<sup>3</sup> Tappeiner;<sup>17</sup> Brandl;<sup>4</sup> Holtz and Schreiber;<sup>6</sup> v. Mering;<sup>11</sup> Morrison, Shay, Ravdin and Cahoon,<sup>12</sup> and others) is actually opposed to this viewpoint. Especially certain experimental work on man (Strauss;<sup>16a</sup> Freund and Steinhardt;<sup>5</sup> Shay, Gershon-Cohen and Fels<sup>14</sup>) supports the idea that glucose can leave the stomach by routes other than its two orifices. The present investigation was designed to examine this problem more closely, using the normal human as the experimental subject. The study is divided into three parts: (a) the disappearance of glucose from the stomach with the pylorus functioning; (b) its disappearance from the stomach and duodenum as a unit; (c) its disappearance from the stomach with the pylorus mechanically closed.

**Method.** (a) *Disappearance of Glucose From the Stomach With the Pylorus Functioning.* To normal human subjects, fasting and after the introduction of a gastric tube, test glucose solutions of widely differing concentration were given by mouth. After a measured time the stomach contents were aspirated; the stomach was then thoroughly washed over an additional period of 5 minutes, and all the recovered material was analyzed for its glucose content. The amount lost was calculated per unit of time and usually expressed as loss in grams per hour. In some subjects a second tube was passed through the pylorus to remain throughout the experiment. As the data in the latter cases were similar to those in the former, they have been included in the results without differentiation.

**Results.** Chart 1 shows the grams leaving the stomach per hour plotted against the product of the volume in cc. and the concentration in gm./100 cc. introduced. This product is used in preference to grams introduced only because it conveys the idea that the grams leaving are proportional to the volume of the solution introduced as well as the osmotic gradient due to concentration. There is a suggested relationship. Such a definite scattering of the points, however, implies that the governing factors regulate the process rather loosely. These factors are discussed in the following sections.

It is more important to note that with higher volumes and concentrations it is not uncommon for the stomach to lose 60 to 120 gm. of glucose per hour. On one occasion 190 gm. were lost. These quantities are significant relative to the data presented in the next section.

**Method.** (b) *Disappearance From the Gastro-duodenal Unit.* Normal subjects were intubated with a tube having two lumens and a terminal balloon on one of them. An attempt was made to keep the balloon in an area just distal to the duodenal-jejunal juncture. To this end the experiment was performed with the subject on a fluoroscopic table and observations as to its location were made at 5-minute intervals. An opening in the second lumen just proximal to the balloon was used for continuous aspiration of the contents as they left the duodenum. In some instances

a second balloon slightly below the first with facilities for aspiration between them was used as a detector for leakage past the first balloon.

Glucose solutions were given by mouth. In some experiments, at the end of a fixed period, usually about 30 minutes, the stomach was emptied. Immediate repeated washes of the stomach and duodenum with water removed any residual glucose within a few minutes. In other experiments absorption was allowed to continue until the duodenal contents were practically sugar-free. When the stomach was washed, the amount of glucose leaving the stomach was calculated in grams per hour.

Subtracting the glucose return of the stomach and duodenum from the amount ingested gave the absorption by the total unit.

## GLUCOSE LEAVING STOMACH

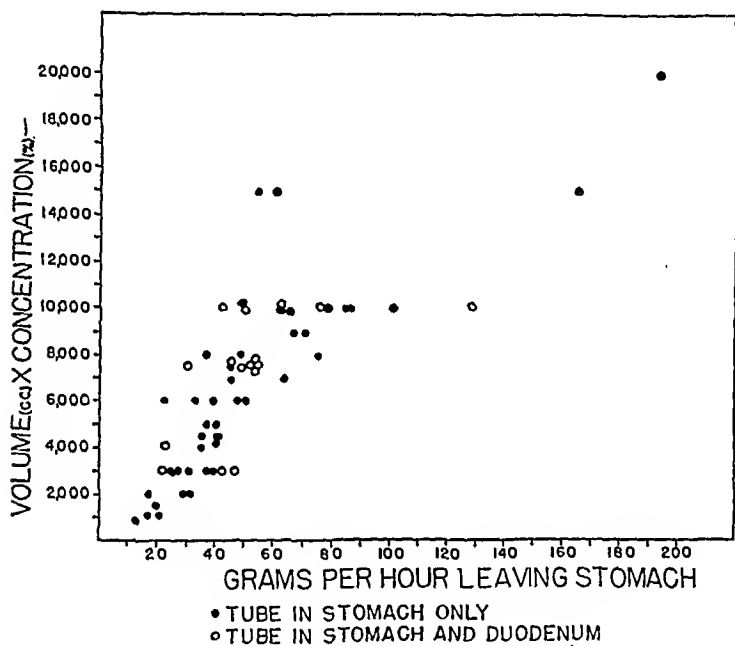


CHART 1.

The material appearing in the upper jejunum was collected in each experiment as a series of specimens, each of which was analyzed separately. The time intervals for each specimen were variable because they were determined by the volume of flow. The total volume of fluid and amount of glucose entering the jejunum were determined.

**Results.** The results of 25 experiments on 9 subjects are shown in Table 1.

**Discussion.** There was a marked inconstancy in the amount of glucose that entered the jejunum from the duodenum. This was noted even in the same individual on different occasions under similar experimental conditions. In most instances it represented only a small fraction of the amount ingested or the amount absorbed

above the duodenal-jejunal juncture. Presumably, therefore, most of the glucose ingested is absorbed above the jejunum while the remainder of the small intestine is available to function when there is excess glucose ingestion, increased motility, decreased absorption, increased hydration, and so on.

TABLE 1.—GASTRO-DUODENAL ABSORPTION OF GLUCOSE.

Subject No.	Case No.	Stomach.		Jejunum.		Gastro-duodenal unit.		
		In		Leaving		Enter	Absorbed	Duration in duod.
		Gm.	%.	Min.	Gm./hr.			
I	207	24	50	..	..	90 1.3	21.5	193
III	220	25	50	..	..	182 3.5	21.5	300
I	211	25	50	..	..	42 1.8	23.7	195
II	219	25	50	..	..	160 2.7	22.3	180?
II	208	25	5	..	..	42 0.8	23.0	195
III	215	25	5	..	..	387 6.9	18.0	213
IV	163	27	5.4	32	36	186 6.8	12.3	38
VII	148A	30	15	34	42	166 5.8	17.9	100
IX	149A	30	15	31	21	106 1.4	9.5	84
VIII	147A	30	15	32	46	67 1.3	23.4	73
IX	149B	40	20	33	21	82 0.3	11.2	63
IV	145	50	25	..	..	74 2.6	47.4	147
VII	146	50	25	..	..	621 19.2	30.8	163
IV	151	75	25	50	48	0 0.0	40.7	60
V	159	75	25	33	51	157 7.7	20.3	40
III	150	75	25	40	53	40 1.2	34.2	73
VI	152	75	25	30	30	71 2.6	12.5	30
IV	161	75	25	32	51	123 7.9	18.4	42
V	162	75	25	33	45	204 13.0	11.9	42
IV	158	75	25	31	52	6 0.3	26.6	37
V	157	100	20	31	42	38 1.1	19.0	37
IV	156	100	33	32	62	101 7.3	25.6	39
V	155	100	33	33	50	195 9.6	16.9	40
IV	154	100	33	172	32	57 2.2	87.9	180
VI	160	150	50	32	55	134 14.4	12.9	37

There was less variation in the amount of glucose leaving the stomach per hour. If, as indicated in the following section, glucose leaves through the stomach wall only in the first short period of contact then this calculation of grams per hour leaving is influenced by the time interval that the glucose is allowed to remain in the stomach.

In general, the amount absorbed by the gastro-duodenal unit varies directly with the amount and concentration of the glucose.

Inspection of the table, furthermore, shows that the absorption for the gastro-duodenal unit is often greater than that anticipated by duodenal absorption<sup>2</sup> alone. Also the amount of glucose which leaves the stomach per hour is often greater than the sum of that usually absorbed from the duodenum<sup>2</sup> and that discharged into the

jejunum from the duodenum. From these observations we may infer that some glucose leaves through the stomach wall.

**Method.** (c) *Disappearance of Glucose From the Stomach With the Pylorus Occluded.* Only professional subjects whose normal health had been assured by physical examination and by the determination of the presence of free acid in the gastric secretion were used. A set of tubes and balloons, the efficiency of which in occluding the pylorus has previously been reported by one of us (Warren<sup>16</sup>), was manipulated into position under the fluoroscope. In some of the experiments a 3-lumened tube was used instead of the double-lumened tube with a thin tube placed parallel with it. The experiments were carried out with the subject either in the supine position or tilted very slightly toward the left side. Through the tube communicating with the stomach cavity solutions of glucose of varying concentration but, with one exception, of constant volume were introduced at body temperature. These were again withdrawn either immediately or at the end of measured periods approximating 30 minutes. At the end of the withdrawal the stomach was washed with tap water in 200 cc. portions while the subject rotated her body until the returning wash was glucose-free as shown by Benedict's qualitative test. The wash usually took about 15 minutes and involved the use of 600 to 800 cc. of water. Throughout the absorption period constant suction was applied in the duodenum beyond the balloons and the resulting accumulated duodenal specimens were withdrawn and tested with Benedict's qualitative solution. In a few of the experiments 10 cc. of 0.5% vital red solution were mixed with the test solution before injection, thus permitting a further check on the escape of gastric contents into the duodenum. Fluoroscopic observations were repeated during and at the end of the test periods. Any experiments in which the duodenal specimens contained glucose or in which the balloons did not stay satisfactorily in place were discarded.

Glucose analyses were carried out by the method previously described.<sup>1</sup> The experimental period was taken arbitrarily as extending from the beginning of the injection of the solution to the onset of the wash. We feel that the contents remaining after the initial aspiration are so diluted by the washes that concentrations well below the isotonic level must be immediately reached as soon as the wash water is introduced. Since other experiments have shown that glucose in such concentrations is not absorbed, it seemed justifiable so to limit the experimental period.

In 6 of the experiments the time period lay between 16 and 37 minutes. One additional experiment, designated by the single asterisk, is added to this group, but is to be mentioned separately because it was not quite so carefully controlled. In 5 experiments the glucose solution was aspirated as quickly as possible after introduction. These are tabulated for comparison alongside the experiments with the longer periods in which comparable concentrations of glucose were used.

**Results.** The results of 12 experiments are listed in Table 2. It is to be noted that the amounts of glucose lost from the concentrations of 11.2% and below were less than 1.7 gm. out of total amounts injected varying between 5.5 and 27 gm. The amounts lost in the other experiments were roughly the same, with the exception of the 40% concentrations, whether the glucose was allowed to remain in the stomach one-half hour or whether it was aspirated

immediately. In other words, the absorption that occurred must have taken place very soon after the injection.

It is apparent from examining the data that the amounts of glucose lost, regardless of the concentration or experimental period, correspond to volumes of from 11 to 30 cc. of the original solution. A control experiment to test whether this might be due to mechanical loss of solution in manipulation of the tubes consisted of injecting and aspirating a 41% glucose solution through the same tube used in the experiments into a rubber balloon and washing out afterwards. It was found that in this procedure only 0.69 gm. was lost, revealing an almost negligible error due to mechanical loss.

TABLE 2.—GLUCOSE ABSORPTION FROM THE STOMACH.

Subject.	Glucose injected.			Glucose recovered, gm.	Duodenal glucose, gm.	Glucose lost, gm.	Experimental period,† min.
	Cc.	%.	Gm.				
C. B.	250	2.46	6.15	5.40	0	0.75	33
C. B.	145	5.0	7.25	6.36	0	0.89	32
F. S.	250	5.0	12.50	11.33	0	1.17	5½
M. H.	250	5.0	12.50	11.95	0	0.55	34
M. P.	245	5.0	12.25	10.61	0	1.64	4
C. B.	254	11.2	28.58	27.08	0	1.50	32
M. P.	250	20.0	50.00	45.37	0	4.63	16
C. B.	250	19.1	47.80	42.60	0	5.20	4½
C. B.*	250	40.0	100.00	86.68	0	13.32	37
C. B.	250	39.3	98.30	91.80	0	6.50	5½
M. P.	249	60.0	149.40	129.65	0	19.75	35½
M. P.	250	60.3	150.80	133.10	0	17.70	7½

\* In this experiment barium mixed with the glucose instead of aspiration of duodenal contents was used to check the efficiency of the block.

† Measured from onset of injection to onset of wash.

**Discussion.** The mechanism of absorption in the stomach has been accepted, by most of those who believe it occurs, as a physical process of diffusion, in contradistinction to the special absorptive process present in the small intestine which enables the mucosa to extract sugar from a hypotonic solution. While Roth and Strauss<sup>13</sup> and Strauss<sup>16b</sup> have defended this physical explanation, others have felt that, were it so, far more sugar would pass through the mucosa than direct observation has indicated.

It is important to note, however, that the concentration of strong glucose a short time after it reaches the stomach varies depending on the location from which the sample is obtained. The stomach is often described as a good mixing organ but it is only because this is not the case that the ingestion of a concentrated solution can be followed so promptly by the evacuation of a dilute solution. As a matter of fact, a definite concentration gradient, highest at the

center of the gastric mass and lowest at its periphery, is rapidly established, a point which is not apparent if a sample of the total mixed gastric contents is taken as indicative of the true conditions within the stomach. This fact is illustrated by the results of an experiment upon a dog. From the stomach, isolated *in situ* and filled with 50% glucose, 2 simultaneous specimens were aspirated 10 minutes later. The concentration of the one from the center of the contents was 40.2% while that from near the periphery was 18.3%. The suggestion is obvious that the concentration of the most peripheral layer actually adjacent to the epithelial cells would have been even lower.

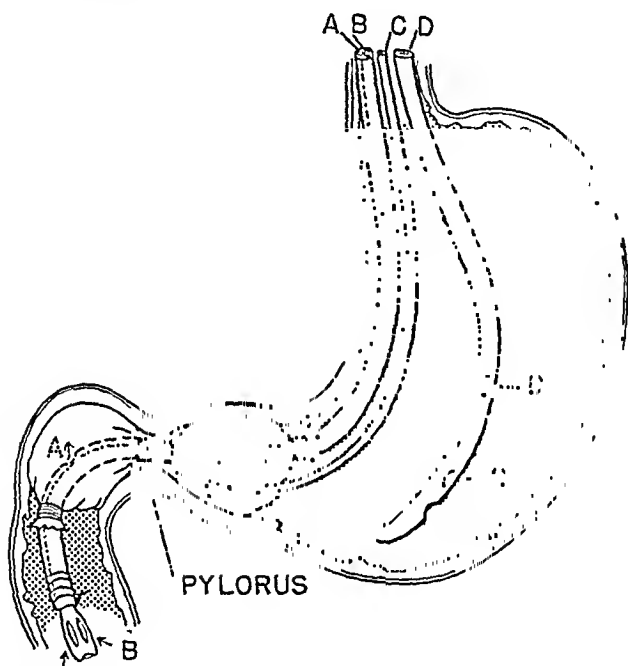


FIG. 1.—Technique of obstructing the pylorus. A, Balloon in duodenal cap and tube lumen through which air is injected into the balloon; B, aspirating tip in duodenum and lumen through which duodenal content is constantly aspirated throughout the experiment; C, balloon proximal to the pylorus and fine tube through which air is injected to distend it; D, large lumened Levine tube for filling and emptying the stomach.

It is also obvious that, if the concentrated glucose contents of the stomach were only separated from the blood and tissue fluids by a membrane permeable to both glucose and water, diffusion would continue as long as the stomach contents were hypertonic. Some other explanation for the cessation of the removal of glucose through the stomach wall seems necessary. We can only conjecture that it may be concerned with the secretion of mucus. Magee<sup>10</sup> and others have shown that there is a marked secretion of mucus in response to the apparently irritating action of strong glucose.

This might form some protective covering over the walls of the stomach through which glucose would diffuse slowly as through a gel.

We are inclined therefore to the view that the stomach is "not adapted" to glucose absorption. When, however, unphysiologic amounts of strong diffusible glucose are ingested its hypertonicity causes a certain amount to pass through or into the stomach wall until in a short time it is inhibited by some mechanism.

**General Discussion.** It is important to differentiate what seems to be the usual mechanism of action of the stomach and duodenum in response to the ingestion of glucose from certain striking variations which may occur in different individuals, or in the same individual under comparable experimental conditions on different occasions. The factors responsible for these variations are obscure. Under the conditions of experimentation reported in Section *b*, glucose did not leave the stomach at a greater rate than 62 gm./hr., while with a greater number of cases, as shown in Chart 1, this figure was often exceeded. That the subjects used for the experiments in Section *b* were selected from coöperative individuals accustomed to intubation may explain the difference.

In the light of these observations and of those presented previously in the series, we may generalize concerning the mechanism involved in the disposal of concentrated glucose solutions ingested into the alimentary canal. As a concentrated solution hits the wall of the stomach a certain amount is removed in the first short period of contact. Equally quickly there occurs a movement of fluid from the mucosa into the gastric cavity, but this does not occur as rapidly as one would anticipate on the basis of simple diffusion through a membrane, and a high concentration of the contents as a whole is well maintained. Only gradually does this decrease as the balance between the movement of fluid into the stomach and of fluid and glucose out of the stomach shifts in favor of increasing dilution. As the gastric contents slowly circulate in response to the mixing action of peristalsis, the peripheral layer moving caudad and the central column orad, that portion entering the antrum is exposed to a rapid change in the conditions that govern this balance. The ratio of mucosal surface to contained solution increases rapidly, until as the glucose reaches the pylorus at the apex of the conical antrum, it is that portion which has been longest in contact with the gastric mucosa that enters the duodenal cap and that which has had least opportunity for dilution that is returned toward the fundus. Whether or not this mechanism alone is accountable, the fact remains that the stomach begins within a few minutes to put out small quantities of its contents at a concentration never observed by us to exceed 15%. In this sense the stomach is seen to be a highly efficient diluting organ, acting as an effective barrier against the entry of highly concentrated solutions into the duodenum. From

the standpoint of the gastric residue, however, it is striking to observe how slowly the concentration of the total mixed gastric contents falls, considering the osmotic gradient existing between it and the body fluids.

When the relatively small volume of glucose at a concentration of 15% or less enters the duodenum, it is almost immediately diluted still further. This is undoubtedly due to a large extent to the relatively large surface area to which it is exposed in respect to its volume. Because of this dilution and the absorption of glucose, if any sugar escapes into the jejunum it is almost never above 6% and its concentration is approaching isotonicity with the body fluids.

Glucose is rapidly absorbed by the duodenum and in many instances its capacity to absorb is sufficient to take care of all the glucose coming from the stomach so that no glucose passes into the jejunum. Previous experiments have shown that if it does pass into the lower intestine it can also be absorbed very readily there. It has been mentioned previously that nature did not intend to compel the gastro-intestinal tract to deal with such concentrated solutions with a high osmotic pressure, but as is here shown, there is a large factor of safety sufficient to handle such solutions with a maximum of safety to the human organism.

**Conclusions.** When concentrated glucose solutions are ingested, a certain amount leaves through the stomach wall during the first short period of contact. Indirect evidence is supported by experiments in which the pylorus is mechanically closed.

The rate at which glucose leaves the stomach is usually influenced by the volume and concentration of the solution ingested.

There is a marked variation in the response of the stomach and duodenum to the ingestion of concentrated glucose in the same and in different individuals.

The stomach and duodenum may often complete the absorption of glucose without the aid of the remainder of the small intestine.

A summary is given which presents the mechanisms involved in the handling of glucose solutions by the gastro-intestinal tract. It is a concluding résumé of this and other preceding papers of this series.

**NOTE.** The recent publication by Shay, Gershon-Cohen, Fels and Munro<sup>15</sup> of the results of experiments directed at the same problems that have concerned us but leading to somewhat different conclusions demand special comment. Any technique for the quantitative study of absorption must provide a method, 1, of recovering completely the unabsorbed fraction of the test material, 2, of starting and stopping the absorption period with maximum abruptness, and 3, of retaining the test solution in contact with the mucosa of the desired area for a given period. The pyloro-duodenal region



is unquestionably the most difficult region of the digestive tract for which to devise such a procedure because of the muscular activity that it exhibits. Though it is to a comparison of these technical points that one must first turn in attempting to weigh the significance of divergent results, not every difference in the conclusions reached is on this basis. Conflicting points of view have at times led to different interpretations being placed on the same facts.

In these experiments the efficiency of balloons in blocking the caudad flow of intestinal contents must be adequately controlled.

If absorption is to be expressed in grams/unit time the duration of the period must be clean cut. It is always easy to start an experiment quickly, but we are inclined to feel that the ideal technique is that which allows the most rapid washing out of the gut at the end of the absorption period, provided that the completeness of the recovery is not endangered. This hinges in part on the caliber of the tube lumens and forced us to the use of devices composed of fine tubes for air and large ones for fluid. Without this, our washes took far too long to perform.

The efforts of the gut to dislodge test solutions are exasperatingly effective. We were not able to prevent regurgitation of fluid from duodenum to stomach and so had to devise a technique that assumed its occurrence and provided for its removal. Neither were we able to prevent the advance of balloons from the duodenum to the jejunum though it was only by frequent fluoroscopy that we appreciated how constantly this took place.

Such differences in method we believe account for the differences in the observed rates of absorption. Differences in point of view only, however, are exemplified by such statements as that the stomach is not a good diluting organ. We would agree that the material retained in the stomach is diluted slowly but we feel that the function of the stomach in this regard is to put out a fluid of low concentration and that this it accomplishes with remarkable rapidity.

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## THE SABIN AGGLUTINATION TEST AND THE POLYSACCHARIDE SKIN TEST (FRANCIS) AS INDICES OF RECOVERY IN PNEUMONIA.

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SULFAPYRIDINE so frequently causes unpleasant reactions, such as nausea and vomiting, that physicians who prescribe it in the treatment of pneumonia are often anxious to discontinue its administration at the earliest moment compatible with uncomplicated recovery. For that reason, a simple test for determining when it is safe to discontinue sulfapyridine is of importance in the management of pneumonia.

In a previous paper,<sup>1</sup> the authors reported the results of their studies on the development of immunity in 50 patients with pneumococcus pneumonia treated with sulfapyridine. We pointed out then that active immunity rarely develops before the eighth day of the disease, and that discontinuing sulfapyridine before that may be unwise. The present report extends that work to include 157 patients, in 151 of whom agglutinin tests (Sabin<sup>2</sup>) were done, and in 107 of whom skin tests with pneumococcus capsular polysaccharide (Francis<sup>2</sup>) were performed. Ninety-one patients received both tests. In this study we have again determined with what regularity and to what degree patients develop agglutinin to the type of pneumococcus causing their pneumonia, and what relationship this bears to the extent of the infection, the course of the illness, and the general condition of the patient. Also, we have compared the Sabin test and the Francis test as indices of immunity.

Table 1 classifies all patients who received either the Sabin or the Francis test, according to the kind of test, and to the kind of treatment. Our remarks are limited to those patients who were treated with sulfapyridine alone.

The Agglutinin Test was performed as follows: A small amount of blood, collected from the patient's ear or finger in a capillary tube, was allowed to clot. The contents of the tube were expelled to a glass slide, using a small rubber bulb such as accompanies a smallpox vaccination

outfit. The clot was lifted off with a hot wire loop, leaving the clear serum. A loopful of formalized suspension of the homologous pneumococcus\* was mixed thoroughly with the serum, allowed to dry in air, fixed with heat, laked with Ruge's solution, stained with carbol fuchsin and examined under oil-immersion magnification. The degree of agglutination was classified as 0 to 4+ (see Fig. 1).

TABLE 1.—ANALYSIS OF CASE MATERIAL.

Treatment.	No. cases.	Francis.	Sabin.	Both.
None . . . . .	2	2	0	0
Sulfapyridine . . . . .	157	107	151	91
Serum . . . . .	33	21	21	19
Total . . . . .	192	130	172	110

The agglutinin test was done on 151 patients, 7 of whom died. Of the remaining 144, all but 11, who were followed to the fourteenth day of illness, developed a 3 to 4+ agglutinin test. The average time at which a strong agglutinin test was first obtained was the tenth day of illness. The earliest time such a test was obtained was the third day of the disease, and the latest was the twenty-first day. These 144 patients were divided into two categories, according to the following criteria: 76 patients who had either bacteremia, involvement of more than one lobe, a septic complication or an associated disease, were called complicated; the remaining 68 were called uncomplicated.

Table 2 shows that complicating factors cause a delay in the appearance of maximum agglutinin (from an average of 8.5 days in the uncomplicated to 12.4 in the complicated cases). This table also indicates that more prolonged treatment is required in the complicated group. The average maximum agglutinin observed in each group was the same—slightly more than 3+.

TABLE 2.—RELATION OF COMPLICATIONS TO AGGLUTININ APPEARANCE.

	No. of cases.	Average maximum agglutination.	Average day maximum agglutination first found.	Average duration treatment.
Uncomplicated cases . . . . .	68	3+	8.5	4.9
Complicated cases . . . . .	76	3+	12.4	7.4
Totals and averages . . . . .	144	3+	10.6	6.0

**The Francis Test.** As performed throughout this study, the Francis test consisted of an intracutaneous injection of 0.1 cc. of a 1:1000 dilution of type-specific capsular polysaccharide.† On the opposite arm was injected a control of 0.1 cc. of physiologic solution of sodium chloride. Readings were made in 10 and 20 minutes. To be positive, there had to be a wheal as well as erythema at the site of injection.

*The Francis Test as an Index of Active Immunity—Its Reliability—A Comparison With the Agglutinin Test.* This test was performed

\* Suspensions of nearly all types of pneumococci were supplied by the Lederle Laboratories, Inc.

† Obtained through the Lederle Laboratories for Types 1, 2, 3, 4, 5, 6, 7, 8 and 14.

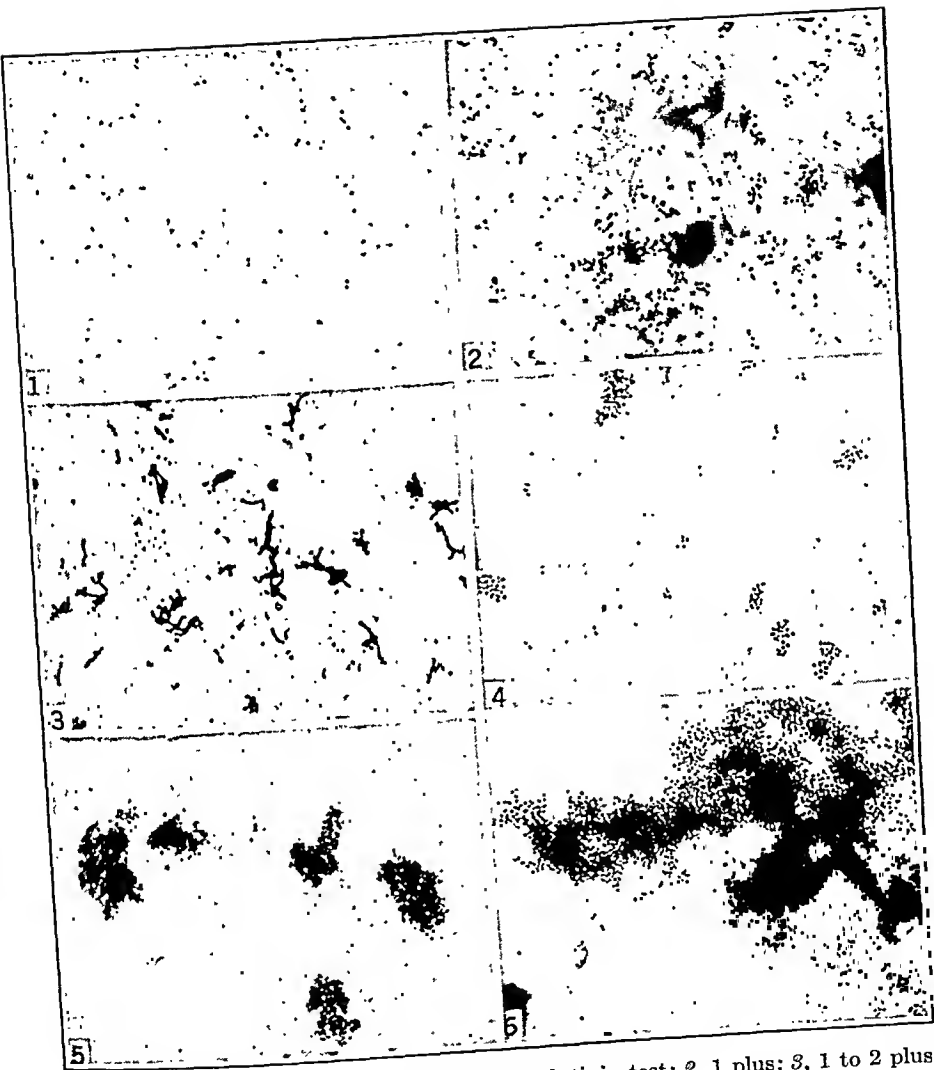


FIG. 1.—The agglutinin test. 1, Negative agglutinin test; 2, 1 plus; 3, 1 to 2 plus; 4, 2 plus; 5, 3 plus; 6, 4 plus.



in 107 patients, 5 of whom died. In 87 the initial test was made before the eighth day of illness; 34 reacted positively to this initial test, on an average of the fifth day of the disease. Eleven of these early reactors to homologous polysaccharide were tested to several heterologous types, and 10 of the 11 reacted to one or more types. From this finding, and from the clinical observation that nearly all of these 34 patients were still critically ill (with high fever and severe toxicity, several with persisting bacteremia) at the time the positive test was obtained, we can conclude that, so far as immunity or increased resistance to the pneumococcus is concerned, these

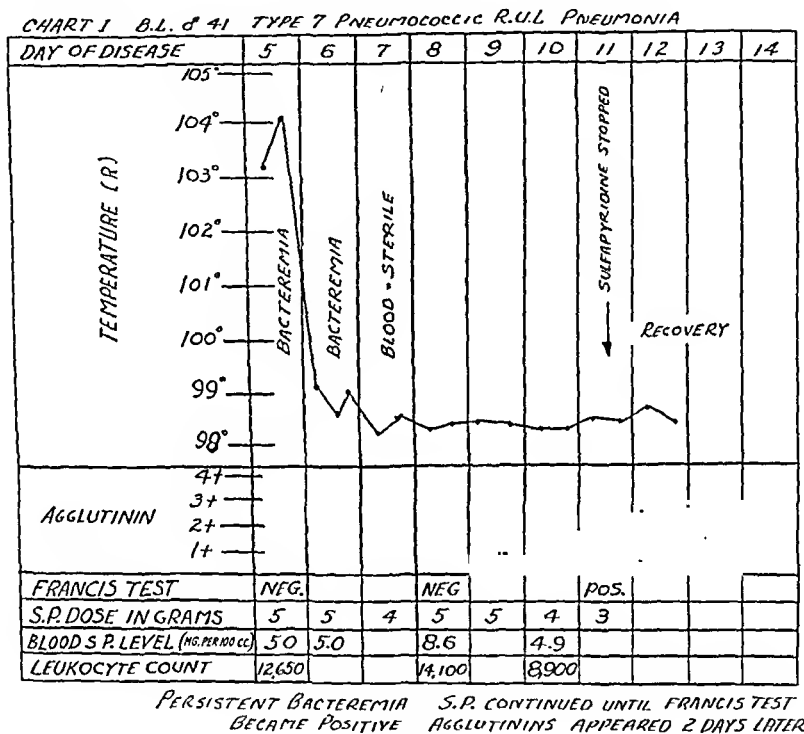


CHART 1.

were "false" positive tests. Fifty-three patients of the 87 tested during the first week of their illness reacted negatively to the initial test. Ten of these remained negative through an average of the fourteenth day of their illness. Two of the 10 patients died. Six of the remaining 8 patients developed a 3 to 4+ agglutinin, and all 8 showed evidence of complete recovery from pneumonia by the end of the second week of the disease. We believe, therefore, that these can be called "false" negative tests. Seven of the 8 were negroes. The character of their skin may account for their failure to exhibit a positive reaction to the injection of the capsular polysaccharide. Four of these patients were skin tested to heterologous

types as well as the homologous type. All reacted negatively. The remaining 43 patients tested during the first week of their illness had an initial negative Francis test, but when it was repeated later in the course of the disease, it reacted positively. In 34 of these patients, agglutinin tests were done simultaneously. The first positive Francis test appeared on an average of 2 days before the agglutinin test became strongly positive (see Chart 1).

For purposes of comparing further the Francis and Sabin tests, an analysis of the tests done day by day was made. Table 3 illustrates the results of this analysis. It indicates that the propor-

TABLE 3.—ANALYSIS OF DAY-BY-DAY RESULTS OF TESTS.

Day of disease:	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13+.	Tot.
Total Francis tests . . .	2	8	27	31	26	30	47	28	32	21	18	24	18	312
No. positive . . .	0	2	11	17	18	17	30	16	20	12	10	11	10	174
Total agglutinin tests	2	17	39	53	64	69	97	90	61	63	56	46	62	719
No. 3 or 4+ . . .	0	0	1	2	5	7	15	27	25	30	21	15	28	176
Agglutinin tests:														
Average reaction	0	0.5	1.1	1.0	1.3	1.4	1.5	2.0	2.2	2.5	2.3	2.3	2.5	

tion of positive to negative Francis tests during the first week of pneumonia was much higher than the proportion of strong (3 to 4+) to weak (0 to 2+) agglutinin tests. Prior to the eighth day of the disease, the average reaction of agglutinin tests was always 1.5+ or less. After the eighth day it was always more than 2+.

Table 4 analyzes 102 patients given the Francis test according to whether or not they were complicated. In those patients whose Francis test was initially negative, and later became positive, there was a significant difference in the duration of illness prior to the

TABLE 4.—RELATION OF COMPLICATIONS TO RESULTS OF FRANCIS TEST.

	No. of cases.	Average day of disease Francis test first positive.	Patients with initial positive Francis test.	Change from - to + occurred in	
				No. of patients.	On day.
Uncomplicated cases . . .	51	7.5	28	15	8.2
Complicated cases . . .	51	8.9	23	21	10.0
Totals and averages . . .	102	8.2	51*	36*	9.2

\* These totals include patients whose initial test was performed later than the seventh day of their illness.

first positive Francis test. In the complicated cases, the average appearance time of a positive Francis test was 2 days later than in the uncomplicated cases, as compared to a difference of 4 days noted with the agglutinin test (see Table 2).

Summarizing the studies on the Francis test, we observed: 1, that 40% of the patients tested during the first week of the disease gave a "false" positive reaction, in several instances to heterologous as well as the homologous type; (2) that approximately 10% gave a "false" negative reaction through the fourteenth day of illness; and 3, that a change from negative to positive Francis test was,

indicative of increasing resistance or active immunity to the pneumococcus. Such a change preceded the development of a significant agglutinin reaction by an average of 2 days, and was delayed for only 2 days by complicating factors.

To understand more fully the factors which influence the development of a strong agglutinin test, we tried to determine why 11 patients failed to develop good agglutinin by the end of the second week of the disease. Four had pneumonia due to Type 7, 3 to Type 1, and 1 each to Types 2, 19, 20 and 23. Of the 11, bacteremia occurred in 4 and confirmed the sputum typing, and in 3 others (one 7, one 1, and the one Type 2), the Francis test changed from negative to positive, which is supportive evidence that the type recovered from the sputum was the etiologic organism of the pneumonia. We cannot feel so sure of the etiology in the other 4 patients, but probably it was correct.\* Eight of the 11 were complicated; average age was 41 years.

For purposes of comparison, we analyzed the records of 17 patients whose 3 to 4+ agglutinin test did not develop until the twelfth day, or later. Type incidence of this group did not resemble that of the group of 11 patients who failed to develop strong agglutinin. There were 8 with Type 2, 4 with Type 1, 2 with Type 8, and 1 each with Types 3, 7, and 14. Thirteen of the 17 were complicated; average age was 40 years.

We are forced to conclude that in these 11 patients, no satisfactory explanation for their failure to develop strong agglutinin could be found. In those 7 who had either bacteremia or a change in Francis test from negative to positive, perhaps a strong agglutinin would have been found if the patients were followed longer than an average of 14 days. For practical purposes, however, we have called these 11 cases "false" negatives, amounting to 10% of all cases

\* That errors in typing may be responsible for failure to obtain a strong agglutinin test or a positive Francis test in an occasional patient is suggested by 2 of our cases. In 1, the initial sputum analysis yielded Type 15 alone. In the course of another investigation, a throat swab culture was made on the ninth day of illness, and was reported 2 days later as containing a predominance of Type 8 pneumococcus, and a few Type 14 and Type 15. This patient had failed to develop more than a 1+ agglutinin to Type 15 up to the twelfth day, but his Francis test to Type 8 was positive and the agglutinin for Type 8 was 4+; Francis test and Sabin test for Type 14 were both negative. In another patient, because the sputum was inadequate for direct typing, a mouse was inoculated. This yielded a mixture of Types 2, 8 and 18 pneumococci. Accordingly this patient was followed with daily Francis tests for Types 2 and 8, and with agglutinin tests for all three types. The Francis test for Type 8 changed from negative to positive on the ninth day and the agglutinin for Type 8 became 4+ on the thirteenth day. Both Francis and agglutinin tests for Type 2 and the agglutinin test for Type 18 remained negative. In both these cases, Type 8 pneumococci were etiologic. This has made us more critical of the view to which we formerly subscribed that when sputum yields more than one type of pneumococcus, the more virulent type is most likely etiologic, and so-called carrier types are unlikely to be the causative organism. Type 8 is such a carrier type; Types 2 and 14 are not; Types 15 and 18 may be. When the blood culture is negative and lung puncture is not indicated, it is impossible always to determine the etiologic type, but development of agglutinin and a change from negative to positive Francis test establishes the etiologic diagnosis.



tested. This compared with 10% "false" negatives with the Francis test.

**Summary.** One hundred and ninety-two patients with pneumococcus pneumonia were studied with either the agglutinin test or the skin test with pneumococcus capsular polysaccharide, or both. Of these, 157 were treated with sulfapyridine alone, and, therefore, constitute a good group in which to study the development of active immunity. In 151 patients in whom the agglutinin test was carried out, it was found that 90% of patients followed to the end of the second week of their illness developed strong agglutinin specific for the type of pneumococcus causing their pneumonia. In the 10% who failed to develop good agglutinin, no satisfactory explanation could be found. These cases were, therefore, called "false" negatives. In those patients who were more seriously ill, there was a delay in the development of strong agglutinin, but when it appeared, it was of the same magnitude as in uncomplicated cases. In 107 patients the Francis test, with the pneumococcus capsular polysaccharide, was performed. Of 87 patients so tested during the first week of their illness, 40% gave "false" positive reactions and 10% gave "false" negative reactions through the fourteenth day of illness. In the remaining 50% of the patients tested in the first week of their illness, an initially negative skin test with capsular polysaccharide was found to become positive later in the course of the disease. The skin test became positive on an average of 2 days before the agglutinin test. The severity of the illness did not delay the development of a positive Francis test as long as it did a strong agglutinin test.

Mention is made of 2 interesting cases in which the etiologic diagnosis depended on the Francis and agglutinin tests.

**Conclusions.** We conclude from our observations, that the agglutinin test is a reliable index to the development of increased resistance to the pneumococcus in the course of pneumonia. It is such a simple test that it may be readily used as a control for sulfapyridine treatment. It rarely becomes positive before the eighth day of the disease; and since in complicated cases it is delayed until the twelfth to thirteenth day, it is particularly important that sulfapyridine be continued longer in such cases. Relapse and late septic complications may be prevented if this is done.

The Francis test is reliable in only 50% of the cases (with the polysaccharide solutions we used). The solutions of polysaccharide are available only for the more common types.

A change from negative to positive Francis test occurs on an average of 2 days before the agglutinin test becomes strongly positive. When this change is noted, it is probably safe to decrease the dosage of sulfapyridine, and to discontinue it 2 days later.

As we concluded in our previous paper, recovery in pneumonia treated with sulfapyridine depends on three factors: an adequate early leukocytosis, an adequately maintained sulfapyridine blood

level, and development of active immunity by the patient for the type of pneumococcus causing his pneumonia. The agglutinin test is a simple, inexpensive, rapid method for determining when active immunity develops.

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### DIAGNOSIS OF THE CAUSE OF AN OBSTRUCTIVE JAUNDICE BY MEANS OF THE BLOOD PICTURE.

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For many years various hematologic tests have been employed for the differential diagnosis between obstructive and hemolytic forms of jaundice. In this connection the fragility of the erythrocytes, the number of the reticulocytes and the character of the van den Bergh reaction are most important. In the cases of jaundice which are found to be due to an obstruction to the outflow of bile, the question then arises as to the cause of this obstruction, and precise diagnosis may here be of considerable importance, as on it depends the advisability of operation.

In the course of carrying out complete and detailed hematologic examinations on patients with obstructive jaundice it occurred to us, because of the marked differences in the blood pictures which we encountered, that one might gain information of diagnostic value as to the cause of the obstruction. We therefore followed such cases until a definite diagnosis was established, and compared the blood pictures in different patients in which the obstruction was due to the same cause. In doing this it soon became apparent that certain changes in the blood were met with almost constantly in those cases having the same etiology. We then ventured to offer a diagnosis as to the cause of the obstruction at the time of the blood study, and found in a large percentage of cases our conclusions turned out to be correct. While this was encouraging, we felt the actual diagnostic value of the information obtained could only be determined if precise rules of diagnosis were laid down and all of a series of cases submitted to them. The results of this investigation are reported below.

Before proceeding with the collection of such a series of cases, it was, of course, necessary to decide upon certain criteria for inclusion of the cases in this group. This was particularly important because obstructive forms of jaundice vary greatly in degree and occur commonly as purely secondary or terminal complications. It was therefore decided that no case would be included in which

the hyperbilirubinemia was less than 1.5 units (0.75 mg. per 100 cc.) or in which the van den Bergh test did not present a strongly positive prompt direct reaction. Moreover, of the cases conforming to this type and degree of bilirubinemia we excluded all those occurring in pregnancy, the newborn and children, acute infections, extensive metastatic involvement of the liver, anemias and other blood dyscrasias, and cases in which the jaundice was distinctly of secondary importance. In other words, we confined the series to persons presenting themselves with a history of jaundice which proved to be of obstructive type and in which the question of the cause of the jaundice naturally arose. Seventy consecutive cases constituted the series.

The hematologic examinations consisted of our usual routine blood studies plus the Takata-Ara test and estimation of the bilirubinemia by means of the Evelyn photoelectric colorimeter. Blood was taken from the patient between 10 and 12 o'clock in the morning and a certain amount of special care was used to obtain very accurate figures for the total and differential white blood cell counts. As usual in our blood studies, the number per cubic millimeter of *each type of white blood cell* was determined. These figures are most important and much more valuable for hematologic diagnosis than the simple relative values given by the percentages.

Although there are a great many possible causes of obstructive jaundice, almost all cases which meet the criteria laid down above consist of one of four conditions. These are malignancy of the pancreas or biliary channels, cholelithiasis, catarrhal jaundice and cirrhosis of the liver. It is the differential hematologic diagnosis between these four diseases with which we are particularly concerned and we shall therefore first present the more or less specific blood changes which we found to occur in each.

In obstructive jaundice due to *malignancy* within or pressing upon the bile channels, the sedimentation velocity of the blood rises. In the majority of cases it reaches figures of over 20 mm. for the first hour, and in fact is often over 30 mm. We employ the method recommended by Wintrobe and, of course, correct for any abnormality in the volume of packed cells. Similarly high readings in the sedimentation velocity may be met with in stone, provided there is an associated relatively acute cholecystitis, and sometimes in advanced cirrhosis, but never to our knowledge in uncomplicated catarrhal jaundice. Should the growth be small with little invasion and destruction of tissue, the increase may be less and the figure after correction lie between 10 and 20 mm. The white blood cells, as a rule, show a certain amount of leukocytosis. This may be only slight or quite marked. The rise is due to an increase in the neutrophils while the lymphocytes fall. This decrease in lymphocytes is a very striking feature in many cases. We have come to use the figure 2000 per c.mm. as our normal base line and consider any count below this as a lymphopenia or at least not a lymphocytosis.

Figures below 1000 are not uncommon. Marked degrees of lymphopenia have never been found in catarrhal jaundice or in cholelithiasis unless there is an associated acute gall bladder condition. It may occur, however, in cirrhosis with anemia and general reduction in all the white blood cells.

In obstruction of the common duct by *stone*, we have found there occurs a lymphocytosis and only a slight rise in the sedimentation velocity. The increase in the total number of lymphocytes may be small but frequently is quite marked with figures around 3000 per c.mm. This is probably due to the low-grade cholecystitis which is usually present. On the other hand, as mentioned above, if there is an associated acute gall bladder infection, the sedimentation velocity rises and the changes in the white blood cell conform to those met with in acute inflammatory processes, namely, a rise in neutrophils with reduction in lymphs.

In *catarrhal jaundice* the hematologic findings are, as a rule, distinctly different. The most outstanding feature is the marked reduction in neutrophils. As the base line for these cells we take 4500 per c.mm. and have found in this condition that they often fall below 3500, with figures from 2000 to 2500 as not uncommon. There is usually a moderate rise in lymphocytes. In addition the blood shows an increased viscosity with relatively high count of erythrocytes and a decreased or normal sedimentation velocity. Only in the rare cases where this condition goes on to a hepatitis or pancreatitis do we find this picture appreciably altered.

In many cases of *cirrhosis* the hyperbilirubinemia is not of the type met with in obstructive jaundice; however, cases do occur in which the van den Bergh test gives a strongly positive prompt direct reaction and differential diagnosis from malignancy and other conditions may be difficult. The changes in the morphologic elements of the blood in this disease are subject to great variation; however, we fortunately have a serologic test in the Takata-Ara reaction which allows us to identify the condition from other members of the group. While it is well recognized that this reaction is not pathognomonic of cirrhosis and may at times be negative in even advanced cases, we have found it extremely valuable and quite trustworthy as a diagnostic aid.

From the results of our studies on a number of these cases, a scheme of differential diagnosis has been drawn up. This purposely confines itself to the hematologic evidence and was made as simple as possible in order that our series might be submitted to a precise diagnostic test. The scheme is reproduced herewith diagrammatically in the accompanying chart and works out as follows: Once a case is established by the other hematologic evidence as that of an obstructive form of jaundice and found to fulfill the criteria outlined above for inclusion in the series, the results of the Takata-Ara test are first considered without regard to any changes in the white blood cells. If this test is positive, the case is imme-

diately diagnosed as a cirrhosis. Faint or plus-minus reactions are considered negative. In our experience, while borderline results are met with, in peri-insular cirrhosis the findings are usually so strongly positive that no question arises.

If the Takata-Ara test is negative, the number of neutrophils per cubic millimeter and the sedimentation velocity are next taken into consideration. If the neutrophils fall below 3000 per cubic millimeter, regardless of the changes in sedimentation velocity, the case is diagnosed catarrhal jaundice. However, if the neutrophils are between 3000 and 4500 it is only given this diagnosis in the presence of a normal sedimentation velocity, that is, not over 10 mm. in the first hour after correction for the volume of packed

SCHEME OF DIFFERENTIAL OIAGNOSIS		RESULTS IN 70 CONSECUTIVE CASES					
		NUMBER OF CASES	POSITIVELY CORRECT	PROBABLY CORRECT	TOTAL	PERCENT	
TAKATA-ARA TEST -							
-	+						
		CIRRHOSIS:-	8	7	1	8	100
NEUTROPENIA { Polys below 4500 ± Normal S. V. All Cases ± Polys below 3000							
-	+						
		CATARRHAL JAUNOICE:-	16		15	15	94
LYMPHOCYTOSIS- (Over 2000)							
	+						
		CHOLELITHIASIS:-	10	4	5	9	90
	-						
		MALIGNANCY:-	36	26	3	29	81
TOTALS:-		70	37	24	61	87	

CHART 1.—Diagnosis of the cause of obstructive jaundice by the blood picture.

cells. All cases therefore with neutrophils over 4500 and those cases with 3000 to 4500 neutrophils plus increased sedimentation velocity are considered negative to this diagnosis.

Should the findings fail to allow for either a diagnosis of cirrhosis or catarrhal jaundice, the number of lymphocytes per cubic millimeter becomes important. If these are over 2000, the jaundice is usually due to cholelithiasis; if, on the other hand, the lymphocytes fall below this figure, it is placed in the group of malignancy. In the cases of jaundice due to stone, as a rule, the lymphocytes rise considerably, while in cancer they often fall below 1000. There are therefore comparatively few cases in these two groups in which the figure is close to the borderline of 2000. In the final or malignancy group, which includes all cases which have not allowed for

a diagnosis of cirrhosis, catarrhal jaundice or stone, one also finds some cases of acute cholecystitis. We found it impossible to separate these by any specific hematologic finding from malignancy, though other clinical evidence usually allows for a ready recognition.

It should be quite obvious that the scheme of differential diagnosis described above must be followed precisely and in the order given, for it is so drawn up that only under those conditions will it be of value in giving information as to the cause of the jaundice.

In the second part of the accompanying chart are given the results which were obtained in the application of the scheme of diagnosis to 70 consecutive cases of obstructive jaundice examined by us which conformed to the specifications laid down above for inclusion in the series. In all of these cases where a positive diagnosis was not obtained by operation, biopsy or autopsy, a special attempt was made to confirm the clinical diagnosis by following up the case after it left the hospital.

In the series of 70 cases, a positive Takata-Ara test was obtained 8 times. Seven of these 8 cases came to autopsy and the diagnosis of peri-insular cirrhosis was confirmed. The other case died at home and no postmortem examination was done. However, the clinical findings and course were always quite typical of this disease and no doubt ever arose as to the diagnosis. This gives a total of 8 correct out of 8 (100%).

Sixteen cases showed the neutropenia and sedimentation velocity to put them in the group of catarrhal jaundice. Of these, 7 had less than 3000 neutrophils per cubic millimeter, while 9 had over 3000, but less than 4500 neutrophils, with normal sedimentation velocity. All of the cases with neutrophils below 3000 were diagnosed catarrhal jaundice clinically on leaving the hospital, and follow-up of these patients has failed to show anything to alter this opinion. One underwent exploratory laparotomy while in the hospital but no other cause for the jaundice was disclosed. Of the 9 cases with neutrophils between 3000 and 4500 and normal sedimentation velocity, 4 were discharged from the hospital with a definite diagnosis of catarrhal jaundice, 4 were considered uncertain but probably catarrhal jaundice. The remaining case was later operated on and a silent stone found in the common duct with a small thickened gall bladder. Follow-up of the other cases showed no reason to alter the diagnosis. This gives a total of 15 out of 16 probably correct (94%).

Of the remaining cases, 10 showed over 2000 lymphocytes per cubic millimeter. The sedimentation velocity in these patients varied from normal to rapid. In 4, stone was found in the common duct at operation. Four others were diagnosed jaundice due to stone, but not operated upon. One was operated on and a large dilated gall bladder removed. No stone was present in the duct, but it was concluded that the jaundice had been caused by a stone

which had passed. The remaining case proved at operation to have a carcinoma of the head of the pancreas. This gives a total of 9 out of 10 probably correct (90%).

The remaining 36 cases had less than 2000 lymphocytes per cubic centimeter and consequently fell into the final or malignancy group. In many the differential white blood cell count showed a marked lymphopenia with less than 1000 per cubic millimeter. Of the 36 cases, the diagnosis of carcinoma was positively confirmed by operation, biopsy or autopsy in 26. In 3 other cases the diagnosis of malignancy was felt to be quite certain, but there was no operation or autopsy. Four cases had acute gall bladder conditions with cholelithiasis. In these there was an increase in the total white blood cells to around 10,000, with the typical differential picture of acute infection (high neutrophils and low lymphocytes) and rapid sedimentation velocity. Of the 3 remaining cases in this group, 1 was operated upon and the obstruction of bile was found due to a fibrosis of the common duct; another was discharged with a probable diagnosis of a catarrhal jaundice which had gone on to a chronic cholangitis; and the third, who refused operation, was sent home without any definite conclusion as to the cause of jaundice being reached. This patient may have had a cancer but we were unable to get any further information through follow-up sources. In this group the diagnosis of malignancy was positively correct in 26 and probably correct in 3, a total of 29 (81%).

Summarizing the complete series of 70 cases one finds the diagnosis positively confirmed by operation, biopsy or autopsy in 37 and probably correct in 24, which includes 15 cases of catarrhal jaundice. This makes a total of 61 out of 70 (87%) in which one feels quite justified in concluding that the hematologic diagnosis according to the scheme presented has given the correct diagnosis of the cause of the obstructive jaundice.

In a number of instances the hematologic diagnosis was found eventually to be correct in cases where the other clinical findings had led to erroneous conclusions. As an example, we had the case of a large fleshy woman of 65 years who was believed to have a carcinoma of the head of the pancreas. A large, tense, dilated gall bladder was apparently palpable. The hematologic findings were those of catarrhal jaundice. Laparotomy was performed and the mass was found to be a Riedel lobe of the liver. She made an uneventful recovery.

In another case, a 50-year-old male was suspected of having malignancy because of the duration and intensity of the obstructive jaundice with marked hyperbilirubinemia. The Takata-Ara test was positive and autopsy revealed a peri-insular cirrhosis. On one occasion where the hematologic findings were those of malignancy, the abdomen was opened and no cause for the jaundice could be found. Autopsy later revealed a small intrahepatic carcinoma at

the junction of the hepatic ducts. Several other interesting examples of the valuable information given by the blood findings might be included.

It is beyond the scope of this paper to enter into a theoretical discussion of the possible explanations for the various blood pictures presented. It is doubtful if it could lead to anything more than hypothetical statements. The scheme of diagnosis presented is essentially an empirical trick based on the findings in a large number of cases. Until our knowledge of the causes for the various changes met with increases, it is better to accept it as such.

**Conclusions.** A scheme for the differential diagnosis of the causes of obstructive jaundice by means of certain hematologic findings is presented. By this method jaundice due to malignancy, jaundice caused by stone, catarrhal jaundice and cirrhosis can usually be readily identified. In a series of 70 consecutive cases the diagnosis based on this evidence was found to be positively or most probably correct in 87%.

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## THE RELATION OF PHOSPHORUS TO FAT AND GLUCOSE METABOLISM IN SPRUE.

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It is the currently accepted view that the sprue syndrome is caused by faulty absorption from the intestinal tract,<sup>3,5,12,13,16,19</sup> though the cause of this defective absorption is not known. The sprue patient absorbs proteins normally, but fats and carbohydrates are poorly absorbed, leading often to secondary deficiencies of vitamins, calcium, phosphorus, and a hematopoietic factor. There are sound reasons for thinking that the absorption of many foodstuffs depends upon phosphorylation,<sup>23</sup> the importance of phosphorus in the intermediary metabolism of carbohydrates is well established, and there is much evidence that it is involved, likewise, in the intermediary metabolism of fat.<sup>18</sup> It was thought, therefore, that a study of the phosphorus metabolism in sprue during the absorption of oil and glucose might give some further information on absorption and metabolism in this condition. Furthermore, it was hoped that the study might give some evidence in support or refutation of the theory proposed by Verzar<sup>22</sup> that the underlying physiologic defect in sprue is a breakdown in the phosphorylating mechanism of absorption.

In the course of a study on the effects of the ingestion of phospholipid upon metabolism<sup>15a</sup> it was found that after the ingestion of



olive oil by normal humans there is a lowering of the serum inorganic phosphorus and decreased urinary phosphorus excretion. This phenomenon has been reported after the ingestion of carbohydrates<sup>2,4,6,8,14,20</sup> where it is thought to be due to a mobilization of phosphorus in the muscles for sugar metabolism, but it does not

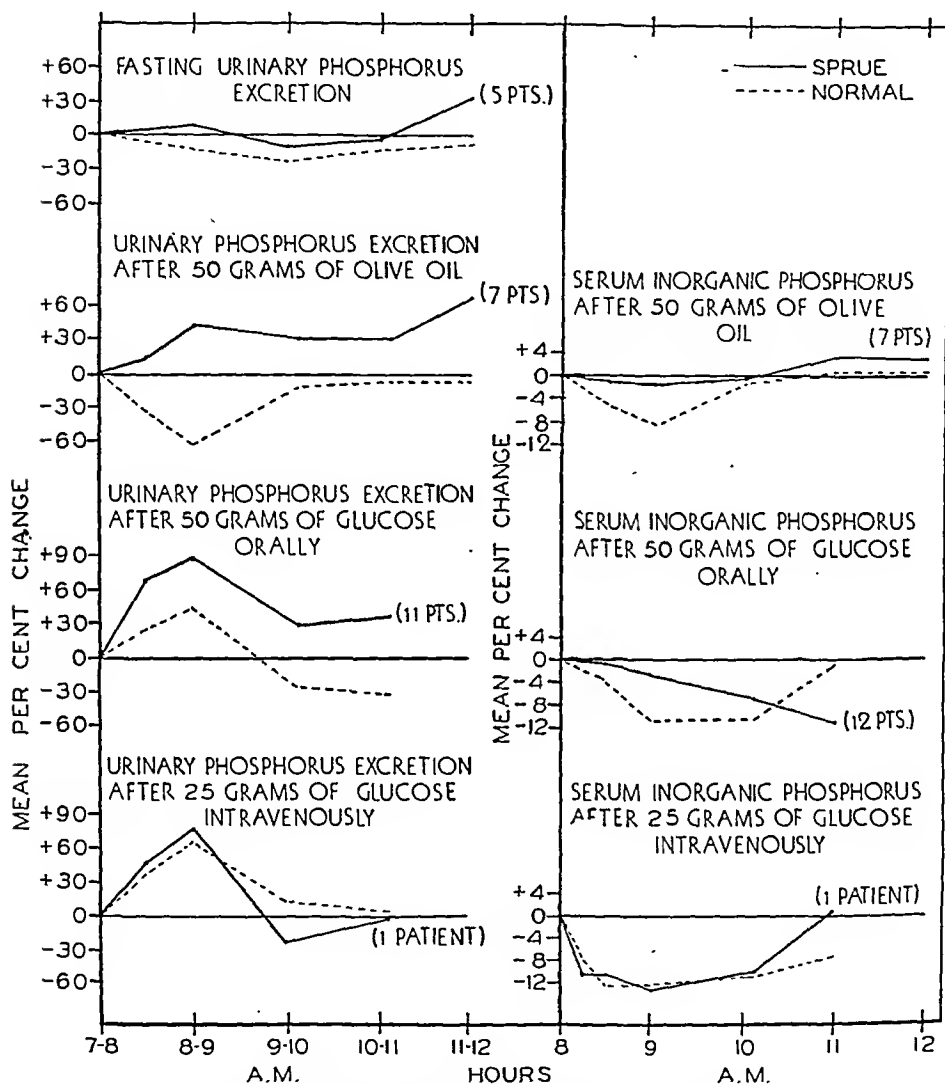


CHART 1.—The relation of fat and glucose absorption to phosphorus metabolism in normal persons and in sprue.

occur after the ingestion of proteins,<sup>9,10,17</sup> in which case, on the contrary, there is an increase in urinary phosphorus excretion.

We then investigated more completely the changes in serum phosphate and rate of phosphorus excretion after the administration of oil and glucose to normal humans and have reported the results elsewhere.<sup>15</sup> Finally, we have made the same observations on

sprue patients and have found considerable variation from the normal after the ingestion of the metabolites, but normal results after their intravenous injection. The respiratory quotient was also determined on sprue patients after meals of oil and glucose.

**Experimental.** All experiments were conducted in the morning approximately 15 hours after the last meal. At 7 A.M. the subjects voided and received a glass of water. Just before 8.00 they again voided and immediately after were given the test meal and a glass of water. Blood and urine samples were taken, and a glass of water given at 8.30, 9.00, 10.00, 11.00 and 12.00. Serum and urinary phosphorus were determined according to the method of Fiske and Subbarow.<sup>7</sup> The respiratory quotient was determined by collecting the exhaled air for 5 minutes in a Douglas bag and analyzing it in an Haldane apparatus.

**Discussion.** The mean per cent changes are reviewed in the chart. The number of experiments vary from 5 for the fasting urinary phosphorus excretion to 13 for the effects of ingested glucose, except that only 1 intravenous glucose tolerance test was performed. The mean values are very representative of the individual experiments. The normal changes<sup>15b</sup> are given for comparison.

The normal phosphorus changes in sprue after intravenous glucose and the close parallel between the degree of elevation of the respiratory quotient and blood sugar after oral glucose (Table 1) are evidence that the sprue patient can metabolize glucose normally after it is in the blood. Consequently, the delayed fall observed in serum phosphorus after the ingestion of glucose by these patients can only be explained on the basis that the sugar reaches the blood stream abnormally slowly, that is, is very slowly absorbed. This does not support Thaysen's theory that the low blood sugar curve is due to abnormally rapid assimilation of the absorbed glucose by the starved tissue.<sup>21</sup>

TABLE 1.—BLOOD SUGAR AND RESPIRATORY QUOTIENT AFTER THE INGESTION OF 50 GM. OF GLUCOSE BY SPRUE PATIENTS.

Hours after sugar.	P. L.		P. L.		L. M.		L. J.*		W. S.		A. B.	
	Bl. sug.	R. Q.	Bl. sug.	R. Q.	Bl. sug.	R. Q.	Bl. sug.	R. Q.	Bl. sug.	R. Q.	Bl. sug.	R. Q.
Fasting	78	0.777	85	0.732	72	0.770	98	0.727	70	0.799	79	0.722
0.5	81	0.806	103	0.875	72	0.835	104	0.779	83	0.790	78	0.753
1.0	91	..	115	0.843	77	0.874	178	0.845	105	0.862	84	0.726
2.0	88	0.783	103	0.876	82	0.861	103	0.800	121	0.923	87	0.774
3.0	87	0.758	89	0.848	73	0.859	91	0.828	93	0.867	95	0.778

\* Patient in remission.

Similarly, the delayed fall in respiratory quotient (Table 2), the correspondingly slight increase in blood fats<sup>1,11</sup> and the failure of any serum phosphorus response after oil ingestion parallel the conditions after glucose ingestion and make it evident that here, too,

the abnormal phosphorus changes result from the failure of the metabolite to reach the blood at a normal rate.

TABLE 2.—THE RESPIRATORY QUOTIENT AFTER THE INGESTION OF 50 GM. OF OLIVE OIL BY SPRUE PATIENTS.

Hours after oil.	L. J.	L. J.	W. S.	W. S.	A. B.
Fasting	0.827	0.776	0.790	0.956	0.748
0.5	0.730	0.792	0.812	0.961	0.743
1.0	0.749	0.770	0.838	0.897	0.763
2.0	0.740	0.716	...	0.813	0.805
3.0	0.746	0.752	0.870	0.803	0.755
4.0	0.731	0.730	0.755	0.841	0.703

The explanation for the increase in the rate of phosphorus excretion in sprue during absorption is not so obvious. However, since it is true that the phosphorus content of the tissues is increased after the ingestion of oil and glucose<sup>8,15b</sup> the presence of food in the intestine may be the stimulus which causes this mobilization. If the food fails to reach the blood, the mobilized phosphorus is excreted.

**Summary.** 1. Sprue patients do not exhibit the normal fasting diurnal variation in phosphorus excretion.

2. After the ingestion of olive oil by sprue patients there is an increase in urinary phosphorus excretion as compared to a decrease in normals. There is no significant change in serum inorganic phosphorus.

3. After the ingestion of glucose by sprue patients the serum phosphorus decreases much more slowly and the urinary phosphorus excretion is much greater than in normals.

4. The changes in blood sugar, serum phosphorus, and rate of phosphorus excretion after the intravenous injection of glucose are of the same order in normal persons and in sprue patients.

5. These findings, as well as the delayed changes in respiratory quotient after oil and glucose meals, reflect the slow rate of intestinal absorption by the sprue patient.

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# THE CENTRAL NERVOUS SYSTEM STIMULANT EFFECTS OF DEXTRO-AMPHETAMINE SULPHATE.

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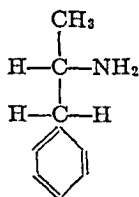
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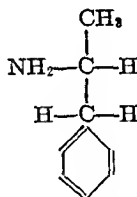
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THE central nervous system stimulant effects of amphetamine (racemic  $\alpha$ -methylphenethylamine or phenisopropylamine, benzedrine, S.K.F.) were noted by Alles<sup>1a</sup> in its awakening effects on anesthetized animals and in its insomnia-producing effect in man. Therapeutic use of the central effects of amphetamine was first made by Prinzmetal and Bloomberg.<sup>14</sup> A large literature has since accumulated verifying these observations and amplifying knowledge with regard to the effects of amphetamine manifested as a result of its stimulant actions upon central nervous system mechanisms.

Amphetamine is a racemic compound and is composed of equal parts of the optically active dextro- and levo-isomers. By suitable means amphetamine may be resolved into its two optically isomeric components which may be represented by the structural formulæ:



Dextro-amphetamine.



Levo-amphetamine.

These two compounds differ in their asymmetry about the second carbon atom on the side chain, just as dextro-ephedrine differs from dextro-pseudoephedrine, or as levo-ephedrine differs from levo-pseudoephedrine. However, the structures of ephedrines and pseudoephedrines each contain two asymmetric centers which also lead to differences in chemical and physical properties other than in their optically rotatory powers.

A study of the comparative physiologic actions of the optically isomeric amphetamines has been reported by Alles<sup>1b</sup> who found their activities upon peripheral nervous system mechanisms to be closely similar. Their central nervous system stimulant effects differed considerably, however, and the dextro-isomer was found to be more active than the racemic or levo-isomers. In experiments on man, following oral administration, the stimulant and insomnia-producing effects of the dextro compound were 2 to 4 times greater

than with the levo compound. Trevan<sup>19</sup> has reported that the analeptic effect of the dextro-isomer is greater than that of the levo-isomer for mice anesthetized with paraldehyde.

It therefore seemed important to determine the effectiveness of dextro-amphetamine in clinical conditions where the central nervous system stimulating effects of racemic amphetamine has been found to be of therapeutic value. From the clinical standpoint, comparison of the dextro and racemic compounds is of chief interest, but comparison of the dextro and levo compounds was also carried out to some extent because of the theoretical interest in the valuation of the ratio of their activities. All compounds were used in the form of their sulphate salts, and administered in water solutions of various concentrations so that the patients received dosages constant in volume and appearance. The subjects were not told what compound they were receiving, and kept accurate daily notes of its effect. By repeated trials of various concentrations of the different isomers, an estimation of the relative effectiveness of each compound was determined. The patient's response was generally first standardized with the racemic sulphate, then the dextro and levo sulphates were substituted and compared. Such a comparative study generally took from 2 to 4 months for each patient, as each compound at each dosage level was usually maintained for a week or more, and repeated in all cases, before drawing conclusions.

*Narcolepsy.* The central nervous system stimulating effects of amphetamine sulphate were used for treatment of this disease by Prinzmetal and Bloomberg<sup>14</sup> and their observations have been confirmed.<sup>15,18,20,21</sup> Freedom from attacks of sleep and practically complete relief from cataplexy are obtained when suitable doses are given. Although narcolepsy is a rare disease, it is an important one for the study of the central effects of this type of drug compound. The beneficial actions are so definite and striking that it is possible to evaluate the relative activities of related compounds with some degree of precision. We have been able to study the effects of the several compounds of interest in 6 cases of narcolepsy. In all instances dextro-amphetamine was found to be much more effective than racemic amphetamine. A summary of the dosages found equally effective is given in Table 1. The average amount of dextro-amphetamine sulphate for all 6 cases was 20 mg. per day, compared with 38 mg. of racemic amphetamine sulphate, or 60 mg. of levo-amphetamine sulphate.

*Postencephalitic Parkinson's Disease.* The effectiveness of amphetamine sulphate in treatment of certain symptoms of patients with postencephalitic Parkinson's disease was observed by Solomon, Mitchell and Prinzmetal.<sup>17</sup> They found that its use in conjunction with stramonium is beneficial in most cases, causing an increase in energy and a decrease in drowsiness and oculogyric crises in all

such cases. In about two-thirds of benefited cases there were decreases in both rigidity and tremor. Similar results have been reported by others.<sup>4,6,9,16</sup> The effects of the amphetamine isomers have been studied by us in 4 cases of postencephalitic Parkinson's disease.

Dextro-amphetamine was found to be of therapeutic benefit in all 4 cases, and a comparison of the relative effectiveness in 2 of the patients showed dextro-amphetamine to be more effective than similar doses of racemic amphetamine or of levo-amphetamine (Table 1).

TABLE 1.—COMPARISON OF EFFECTS ON NARCOLEPSY, POST-ENCEPHALITIS IN PARKINSON'S DISEASE AND POSTURAL HYPOTENSION.

			<i>Narcolepsy.</i>		Effective daily dose.		
Case.	Sex.	Age.	Daily sleep attacks without medication.	Daily attacks of cataplexy—no medication.	Dextro (mg.).	Racemic (mg.).	Levo (mg.).
1	F	36	4-6	4-6	28	45	70
2	F	34	4-6	1-2	26	52	
3	M	22	4-6	Occasional	25	50	
4	F	30	4-15	None	20	40	80
5	F	27	3-4	Occasional	12.5	25	50
6	M	25	1-3	Occasional	10	20	40
Average for cases of narcolepsy . . . . .					20	38	60

			<i>Post-encephalitic Parkinson's Disease.</i>		Effective daily dose.		
Case.	Sex.	Age	Symptoms.		Dextro (mg.).	Racemic (mg.).	Levo (mg.).
7	M	31	Drowsiness, rigidity, tremor and oculogyric crises		25	40	50
8	M	54	Tremor, rigidity, and oculogyric crises		20	40	

			<i>Postural Hypotension.</i>				
Case.	Sex.	Age	Symptoms.		Dextro (mg.).	Racemic (mg.).	Levo (mg.).
9	M	34	Weakness, dizziness upon assuming the upright position . .		5	10	20

*Postural Hypotension.* One of the authors of this paper<sup>13</sup> reported that amphetamine sulphate relieved the symptoms of a patient with postural hypotension, and others<sup>3,8</sup> have confirmed these results. It was observed that, although the compound relieved the symptoms of the disease, it had but little effect on the fall in blood pressure on assuming the upright position. Paredrine hydrochloride, a compound which tended to stabilize the blood pressure but which has no central nervous system stimulating effect, had little or no effect on the symptoms. It therefore appeared that the beneficial effect of amphetamine sulphate is not primarily due to a rise in blood pressure, a suggestion occasionally offered. In 1 carefully studied patient with postural hypotension (Case 9), the dextro compound proved to be twice as effective as the racemic

compound and 4 times as effective as the levo compound in alleviating his symptoms (Table 1). The relief of the symptom of dizziness had no obvious connection with the effect of the drugs on his blood pressure.

*Effect on Dizziness.* We have observed that the central nervous system stimulating action of these compounds was helpful in alleviating dizziness in several patients without obvious organic disease, though most of these subjects had hypotension. Benefit was also obtained in 2 patients with Ménière's syndrome. The improvement in these patients was not associated with an elevation of blood pressure. Indeed, paredrine hydrochloride, a compound with no central nervous system stimulating effects but with more marked pressor effect, has no therapeutic effect in these subjects. The mechanism of relief is therefore similar to that found in patients with postural hypotension. Because of the difficulties of adequate control, a comparison of the various isomers of amphetamine was not made in this group of patients.

*Depressed States.* Amphetamine sulphate was found to be useful in certain cases of depression by Guttman<sup>7</sup> and by Meyerson.<sup>10</sup> Their observations have been confirmed and extended by others.<sup>2,11,22,23</sup>

An evaluation of central nervous system stimulating drugs in patients with depression is extremely difficult to perform because of the marked spontaneous fluctuations in this condition. We have found that dextro-amphetamine had therapeutic benefit and usefulness in 4 patients with simple depressions. The following case, referred by Dr. Emanuel Libman of New York City, showed a greater benefit from the dextro compound than with larger doses of the racemic amphetamine.

A 54-year-old white male had had periods of depression for about 10 years. The depression was much worse in the morning and would gradually wear off during the morning. The patient worried a great deal about his condition and contemplated giving up the practice of law because of it. He was given 5 mg. per day of racemic amphetamine sulphate with marked improvement in his condition, so that he had no difficulty with his work. After several months, he was given a solution of dextro-amphetamine sulphate. A dosage of 3 mg. of this compound had a greater stimulating effect than 5 mg. of the racemic compound.

*Stimulating Effects in Normal Persons.* That racemic amphetamine sulphate "stimulates" most normal individuals has been observed by most persons using this drug. There is often a feeling of exhilaration, increased confidence, euphoria, loquaciousness, and insomnia. Nathanson<sup>11</sup> has reported an extensive study of the stimulant effects of racemic amphetamine in normal persons.

A comparison of the stimulating effects of dextro- and racemic amphetamine sulphate was made on 13 normal persons who took 2.5 mg. of the dextro and racemic compounds on alternate days in

solution.\* The subjects were all doctors or nurses of the Los Angeles County Hospital. They were not told what compound they were receiving, but were asked to pay attention to the degree of mental stimulation produced.

Of the 13 cases, 12 reported that the dextro compound had a definitely greater stimulating effect than the racemic compound. In only 1 case did the subject experience difficulty differentiating the two compounds. It is of interest that some individuals noticed no effect from 2.5 mg. of the racemic compound, but noticed stimulating effect from the same dose of dextro.

TABLE 2.—COMPARISON OF EFFECTS ON NORMALS.

Case.	Sex.	Dose taken racemic (mg.).	Effects.	Dose taken dextro (mg.).	Effects.
1	F	2.5	Felt less tired	2.5	Greater effect—more pep, loquacity, some sleeplessness that night
2	F	2.5	Felt less tired at end of day	2.5	Less fatigue than with racemic; very thirsty
3	F	2.5	No effect	2.5	Nasal and oral mucosæ very dry; very thirsty for 1 hour afterward
4	F	2.5	No effect	2.5	Very nervous—thirsty; mouth dry for 1½ hours
5	F	2.5	No effect	2.5	No effect
		5.0	No effect	5.0	Slightly nervous—vague stimulation
6	F	2.5	No effect	2.5	Felt more energetic—not so tired
7	M	2.5	More awake for about 1 hr.	2.5	Similar effect, perhaps more awake
		5.0	Slight stimulation	5.0	Mouth dry; vaguely stimulated
8	M	2.5	Mentally more active; no fatigue until late at night	2.5	Excitement; greater mental and physical activity; mouth dry; nervous; moved quickly; garrulous
9	M	2.5	No effect	2.5	No effect
		5.0	No effect	5.0	Hyperexcitable, loquacious, jittery
10	F	2.5	Increased activity—then "let down"	2.5	Less stimulation than with racemic
		5.0	Not conscious of any effect	5.0	Excited, nervous, jittery; dry mouth and very thirsty
11	M	2.5	No effect	2.5	No effect
		5.0	No effect	5.0	Mental lift—less fatigue; moved faster than usual
12	M	2.5	No effect	2.5	Hyperactive and loquacious
13	M	2.5	Slight mental stimulation	2.5	Greater muscular and mental activity; thirsty, better appetite

*Pressor Effects.* Comparison of the pressor effects in normal persons of the dextro-, racemic and levo-isomers of amphetamine was reported by Alles.<sup>16</sup> Following oral administration of the compounds in doses of 10 and 20 mg. doses, their pressor responses were quite closely the same. In resting persons, usually as little as 10 mg. of the sulphates of these isomers causes a definite pressor response, but some apparently normal individuals may not show definite pressor responses even after administration of 20 mg. of racemic amphetamine.

Pressor studies were systematically carried out with only 2 narcolepsy cases, since such observations have little value unless the

\* These observations were made with the aid of Dr. Harvey Lewis.



persons remain at rest throughout the period of observation. Case 1, who had a resting blood pressure level of about 92/70, showed no definite changes in the systolic or diastolic level following 30 mg. of the dextro-, racemic or levo-amphetamine sulphates, although one-half of this amount in single doses of the dextro or racemic compounds exerted marked antisleep effects. Case 4, who had a resting blood pressure of about 100/68, showed no definite pressure changes following 30 mg. of the racemic amphetamine sulphate, although one-half of this amount in a single dose exerted definite antisleep effect.

**Discussion.** It is of interest that similar results were obtained on all subjects studied. The dextro-amphetamine sulphate proved much more active than the racemic compound in the cases of narcolepsy, postencephalitic Parkinson's disease, postural hypotension, simple depressions, and in normal individuals. Reviewing the entire series, it is possible to make an evaluation of the comparative strength of the various compounds by averaging all cases where a comparison was made. The dextro-amphetamine sulphate is approximately  $1\frac{1}{2}$  to 2 times more active than the racemic compound, and 3 to 4 times more active than the levo compound.

Because of the vascular effects of racemic amphetamine it should be used with caution in patients with hypertension and it may precipitate an anginal attack in certain cases of angina pectoris.<sup>12</sup> For an equivalent central stimulant effect, a smaller dose of the dextro-isomer is required and therefore will exert less vascular effect than is obtained with a larger dose of the racemic compound, and its use would seem to be clearly indicated with patients who may derive untoward vascular responses from racemic amphetamine.

It is of interest to note that the lethal dosages for mice of the dextro-, racemic and levo-isomers are closely the same.<sup>16</sup> Therefore, if a given desired result can be obtained from the dextro compound with one-half the dose required of the racemic form, the ratio between the therapeutic and lethal dose is decreased by one-half. Although the ratio of therapeutic to lethal dose would appear to be somewhere between 1:100 to 1:1000 with racemic amphetamine,<sup>5</sup> the further decrease in the ratio may be of some clinical significance.

From these results it would appear that for central nervous system stimulation dextro-amphetamine is a more desirable drug than racemic amphetamine, particularly if there is evidence that the racemic compound does cause undesirable circulatory responses in a given individual. Conversely, it is to be expected that levo-amphetamine would be a more desirable drug than racemic amphetamine when the therapeutic objective is vasoconstriction or other stimulation of peripheral sympathetic nervous system mechanisms.

It seems quite clear from the relation that exists between dextro- and levo-amphetamine that the central nervous system stimulating

effects are unrelated to systemic pressor effects. Paredrine, the para-hydroxy derivative of amphetamine, has greater cardiovascular effects than amphetamine but is without notable effect in stimulating the central nervous system. The failure to note any pressor changes in the narcoleptics, studied at dosage levels sufficient to result in marked antisleep effects, is perhaps more direct proof of the independence of these two effects of amphetamine. That amphetamine has central actions other than on the sleep center is indicated by its causing relief of oculogyric crises in Parkinson's disease and of the cataplexy of narcolepsy.

**Conclusions.** 1. A study was made of the central nervous system stimulating effects of dextro-, racemic and levo-amphetamine sulphates in subjects with narcolepsy, postencephalitic Parkinson's disease, postural hypotension and simple depression.

2. The central nervous system stimulation induced by these compounds is useful in the treatment of dizziness in certain patients.

3. Comparison of the central stimulant effects of dextro- and racemic amphetamine sulphates was also made on normal individuals.

4. It was found that the central effects of the dextro-isomer are approximately  $1\frac{1}{2}$  to 2 times that of the racemic isomer, and 3 to 4 times that of the levo-isomer.

5. The pressor effects of the dextro-, racemic and levo-isomers are closely the same in normal persons.

6. A smaller dose of dextro-amphetamine sulphate can be employed than with the racemic compound for therapeutically useful central stimulant effects with correspondingly less cardiovascular effect and a greater factor of safety.

**Case Reports.** CASE 1.—W. K., a 36-year-old married woman, referred to us by Dr. John Ruddock, had a typical history of narcolepsy beginning after an attack of influenza 11 years ago. There was no history of encephalitis or head injury. Physical and neurologic examinations were non-contributory. Basal metabolic rate determinations during the course of the past 11 years fluctuated from  $-18\%$  to  $0\%$ . Thyroxin had been tried therapeutically without success. Dosages of  $\frac{3}{8}$  and  $\frac{1}{4}$  gr. of ephedrine had been tried 3 years ago, which caused faintness and pounding of the heart. Without any medication, she has as many as 4 to 6 sleep attacks a day and a like number of attacks of cataplexy. The effects of the compounds tested are given in Table 3.

CASE 2.—P. L., a 34-year-old married Mexican woman, referred to us by Dr. Eugene Ziskind, has had narcolepsy and cataplexy since the age of 13. The attacks of sleep are worse during her menstrual periods and after her meals. She has an average of 4 to 5 sleep attacks and 1 to 2 cataplectic attacks a day. There was no history of head injury or encephalitis. Other than obesity, the general physical and neurologic examination was non-contributory.

This patient was initially given 15, 15 and 10 mg. per day of racemic amphetamine sulphate, which reduced her sleep attacks to 4 per week. Following this, she was given 10, 10 and 6 mg. daily of the dextro-isomer, and she fell asleep but once in the week. The following week a daily dosage

of 20, 20 and 12 mg. of the racemic compound was taken, and she fell asleep but once. After a 2-month interval, a second set of comparisons were made, in which she had 1 sleep attack on 15, 15 and 10 mg. daily of the dextro-isomer, while on 20, 20 and 12 mg. daily of the racemic compound she had 8 sleep attacks.

TABLE 3.—EFFECT OF AMPHETAMINE ISOMERS ON ATTACKS OF SLEEP AND CATAPLEXY OF CASE 1.

	Amphetamine isomer.	Daily doses (mg.).	Attacks in week.		Sleep at night.
			Sleep.	Cataplexy.	
10/22-10/28	Racemic	15, 15, 5	3	0	O.K.
10/29-11/4	Dextro	10, 10, 3	1	0	O.K.
11/5-11/11	Racemic	15, 15, 5	7	4	O.K.
11/26-12/2	Levo	30, 30, 10	4	0	O.K.
12/3-12/9	Dextro	12, 12, 4	2	0	O.K.
12/10-12/16	Racemic	20, 20, 6	4	1	Light
12/24-12/30	Dextro	12, 12, 4	4	3	O.K.
12/31-1/6	Racemic	20, 20, 6	2	0	O.K.
1/7-1/13	Dextro	15, 15, 5	0	0	Poor
1/14-1/20	Levo	30, 30, 10	2	0	O.K.
1/28-2/3	Racemic	20, 20, 6	2	0	Poor

CASE 3.—D. M., a 22-year-old single man, referred to us by Dr. S. J. Sperling, has had a typical history of narcolepsy of 6 years' duration, with occasional attacks of cataplexy. He has been unable to retain any job because of frequent sleep attacks which occurred 4 to 6 times daily. There was no history of head injury or encephalitis. The general physical and neurologic examination was non-contributory.

CASE 4.—F. B., a 30-year-old single woman, referred to us by Dr. Eugene Ziskind, had encephalitis 16½ years ago. Since this time she has had frequent daily attacks of sleep and irritability. She has never had any symptoms of Parkinson's disease nor has she had cataplectic attacks. She had no tremor, rigidity or oculogyric crises. The basal metabolic rate was +3%. Physical and neurologic examinations were non-contributory.

CASE 5.—D. M., a 27-year-old married colored woman, referred to us by Dr. Paul Fitzgibbon, has had narcolepsy as long as she can remember. The condition has become worse during the last 6 or 7 years and at present she falls to sleep 3 to 4 times daily, and suffers from cataplexy during excitement. During one pregnancy the condition was worse. Physical and neurologic examination was essentially negative.

CASE 6.—A 25-year-old single Mexican man, referred by Dr. Paul Fitzgibbon, has had narcolepsy for at least 10 years. He has received several head injuries. In his youth he was kicked by a colt and fell from a horse. He generally has 1 to 3 sleep attacks daily and occasional attacks of cataplexy. Physical and neurologic examinations were non-contributory.

CASE 7.—R. B., a 31-year-old single man, referred to us by Dr. Eugene Ziskind, has had typical postencephalitic Parkinson's disease for 3 years. Without medication, he exhibits marked drowsiness, rigidity and tremor, and usually has several attacks of oculogyric crises daily. Other than the rigidity and tremor, his physical and neurologic examination was negative.

The method of study in this patient was to present him with two bottles of solutions to be used on alternate days during the week. The volumetric dosage was kept constant, but the concentrations and contained compound were varied, and the patient kept a daily record of sleepiness, oculogyric crises, and subjective estimations of energy. Comparison of 20 mg.

dosages of the dextro- and racemic amphetamine sulphates showed the dextro-isomer to be clearly the most active. In comparison with 20 mg. of the dextro-isomer, 30 mg. of racemic amphetamine was less effective and 40 mg. was more effective. The effects of 25 mg. daily of the dextro-isomer was matched by 40 mg. of the racemic compound, or by 50 mg. of the levo-isomer.

CASE 8.—B. S., a 54-year-old married man, referred to us by Dr. Ben Newman, has had typical Parkinson's disease for 1½ years. Although there was no history of encephalitis or influenza, it was believed that the patient probably had the postencephalitic type of the disease because of the therapeutic response to central nervous system stimulating drugs, because the patient's son developed Parkinsonism at the same time, and because of frequent ocülogyric crises. Other than the typical mask-like face, tremor, and rigidity, the physical and neurologic examination was essentially non-contributory.

The same method of comparison of the dextro- and the racemic compounds was used as in the above case. It was found that 25 mg. of dextro-amphetamine had a more powerful central stimulatory action than 40 mg. of the racemic compound. The patient was unable to distinguish a difference between the central nervous system stimulating effects of 20 mg. of the dextro- and 40 mg. of the racemic amphetamine.

CASE 9.—R. G., a 34-year-old single man, referred to us by Dr. A. M. Hoffman, had noticed attacks of weakness, dizziness and occasionally syncope for the past few weeks. The symptoms usually occurred when the patient changed from the supine to the upright position. Physical and neurologic examination was essentially negative except that his blood pressure dropped from 120/80 mm. to 70/50 mm. on changing from the recumbent to the upright position.

With this patient it was found that a daily morning dosage of 10 mg. of racemic amphetamine sulphate prevented the attacks of dizziness and weakness without any disturbance of normal sleeping habits. A dosage of 15 mg. of the racemic compound was not notably superior, so the effects of 10 mg. was made the basis of comparison. Daily dosages of 5 and of 6 mg. of the dextro-isomer, or 20 mg. of the levo-isomer, produced comparable effects.

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## INFLUENZAL MENINGITIS TREATED WITH SULFAPYRIDINE.

## BILATERAL URETERAL OBSTRUCTION, UREMIA, RECOVERY.

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THE discovery of a new drug is apt to be followed by the publication of reports of successes, failures and side-effects observed in patients to whom the drug has been administered. This has been true to an unusual degree in the case of the sulfonamide derivatives. Although we hesitate to add to the flood of literature which has followed in the wake of the discovery of sulfapyridine, yet we believe that the case herewith described is of sufficient importance to warrant our reporting it.

**Case Report.** A white female, aged 13, had been deaf since she recovered from an attack of cerebrospinal meningitis at the age of 7. A year later she developed an attack of frequent painful urination accompanied by right lumbar pain; a urinalysis at this time was negative and she apparently recovered completely. Two weeks before her present admission, she complained of earache and appeared feverish, but was able to return to school on the following day and had no further complaints until 2 days before admission when she contracted what appeared to her mother to be gripe. On the following day she went to school, but began to feel chilly, developed headache and vomiting and was put to bed. Vomiting continued, and on the following day, February 7, 1940, her neck became stiff and painful and she was admitted to the Episcopal Hospital.

Examination revealed a well-developed, extremely ill and restless girl with flushed cheeks and herpes labialis. The temperature was 104.3°F. The pulse and respiration rates were 132 and 20 respectively. She soon became irrational and her neck more rigid. The rest of the examination was negative; Kernig's and Brudzinski's signs could not be elicited. There were no petechiæ. Lumbar puncture yielded turbid fluid under 19 mm. of mercury pressure containing 6050 cells per c.mm., all of them neutrophils. The protein content of the fluid was increased (+4) and the sugar was 50 mg. per 100 cc. By direct smear, a pleomorphic Gram-negative bacillus was revealed which on culture was identified by Dr. W. P. Belk as *Hemophilus influenzae* (Pfeiffer's bacillus). A blood culture yielded the same organism. The blood count revealed 31,000 leukocytes, 96% of which were polymorphonuclears and the rest lymphocytes. The urine was negative.

Four hours after admission, she was given 2 gm. (30 gr.) each of sulfapyridine and sodium bicarbonate, and thereafter 1 gm. of each of these drugs every 4 hours night and day. A second lumbar puncture on the following day yielded fluid under 14 mm. Hg pressure with 3648 cells per cubic millimeter, 38% of which were neutrophils and 12% lymphocytes.



FIG. 1.—Partial recovery. Urogram 12 days after complete bilateral ureteral obstruction from sulfapyridine therapy. Shows slight excretion of dye from swollen right kidney. Left kidney has apparently returned to normal.



FIG. 2.—Urogram 12 days later, showing good concentration and excretion by both kidneys, with moderate hydronephrosis and clubbing of some of the calyces of the right, probably due to previously existing ptosis.

The protein was increased (+1) and *Hemophilus influenzae* was again secured by culture, though no organisms were seen in the direct smear. Two days later her temperature had dropped to normal, the spinal fluid was sterile and contained only 90 cells, and the blood culture was sterile. In spite of the dramatic response to sulfapyridine therapy, fearing the possibility of a relapse, the drug was continued in full dosage, until, on February 17, having received 47 gm. of sulfapyridine, she vomited and complained of pain in the right flank. Abdominal examination revealed a tense, tender, freely palpable mass corresponding to the right kidney. The ease with which this mass was felt indicated a marked renal ptosis. With the hope of relieving a possible obstruction of the right ureter, cystoscopy was promptly undertaken.

*Cystoscopy.* The tolerance and capacity of the bladder appeared normal. Lying on the bladder floor was seen considerable putty-like débris streaked with blood. With close observation this material presented a golden sandy appearance. Extruding from the left ureteral orifice was seen a blood clot. Active peristalsis of both ureteral orifices was noted, and there was an occasional sluggish ejection of bloody urine from the left. No urine appeared from the right orifice during the examination. There was no evidence of indigo carmine from either side in 15 minutes. Attempts to catheterize the right ureter revealed a complete block at the 2.5-cm. level, and this obstruction could not be passed. A No. 4 ureteral catheter was passed with some difficulty to the 22-cm. level up the left ureter. There was free drainage of bloody urine through the catheter. This catheter was unfortunately withdrawn with the optimistic thought that the left ureter would remain patulous.

During the next 24 hours she was completely anuric. The blood urea nitrogen, which on admission had been normal, rose to 55, and a generalized convulsion lasting for 2 minutes occurred. The blood pressure was 105 over 78, the temperature 100° F., and the pulse and respiratory rates 92 and 18 respectively.

Because of these developments ureteral catheterization was again attempted. On passage of the cystoscope, approximately 8 cc. of very bloody urine was drained from the bladder. The putty-like débris of the first examination was again noted. A No. 5 ureteral catheter was passed to the 6-cm. level up the left ureter and met an obstruction at this point. With the catheter at this level, hot sterile distilled water was gently forced through the catheter but without effect. The catheter was withdrawn and after manipulation a No. 7 ureteral bougie was finally passed to the left renal pelvis. Upon withdrawal of this a No. 5 ureteral catheter was passed to the left renal pelvis, which resulted in a free drainage of urine. The catheter was left *in situ*. Attempts to relieve the right ureteral obstruction were again unsuccessful. During the next 24 hours 950 cc. of alkaline urine of low specific gravity containing abundant albumin and erythrocytes and leukocytes was passed through the catheter.

During the next 15 days the patient had fever ranging from 99° to 104° F., but the urinary output was satisfactory. On February 20 the ureteral catheter was removed. The urine passed immediately thereafter was very cloudy, containing shreds, débris, many pus cells and frequently erythrocytes.

On February 29 an intravenous urogram (Fig. 1) showed a normal left urinary tract, while the 30-minute film on the right revealed faint evidence of the dye with marked hydronephrosis and ptosis.

On March 12, following steady improvement, a second intravenous urogram (Fig. 2) revealed good concentration on both sides, the left tract being normal. The right showed moderate dilatation of the renal pelvis and early clubbing of the minor calices, presumably due to preëxisting ptosis.



The patient was discharged on March 15 in good condition. Examination in the "Follow-up Clinic" on April 19 revealed no symptoms and the patient in good health.

**Comment.** A search of the literature of 1938 and 1939 has revealed seven reports<sup>3,9,12,13,15,16,22</sup> concerning the use of sulfapyridine in the treatment of 25 cases of meningitis due to *Hemophilus influenzae*, with 14 recoveries.\* This mortality of 44% is in marked contrast with the mortality of 82% and 98% respectively in cases treated with and without specific serum.<sup>7</sup> Sulfanilamide, too, has been used with and without serum,<sup>5,6,11,17,19,20,22,23</sup> but the results are not as impressive as with sulfapyridine.

Ureteral obstruction is a well-recognized complication<sup>2,4,10,21</sup> of sulfapyridine therapy. From animal experimentation<sup>1,8</sup> and clinical observation<sup>14,18</sup> it has been learned that acetylated sulfapyridine crystals frequently are excreted by animals and human beings receiving the drug. In most cases they are no doubt harmless, but when present in excess they may irritate or obstruct the collecting tubules or upper urinary tract, leading to hematuria or anuria, largely if not wholly mechanical in origin. The blood clots themselves, no doubt, may be a factor in the production of obstruction; in our case a mixture of blood clots and crystals could be seen obstructing the left ureter. The fact that the conglomerate mass could not be dislodged by ureteral lavage with warm water is not surprising since acetylated sulfapyridine crystals are poorly soluble in water and are probably rendered more insoluble by the admixture of coagulated blood. Only by manipulation of the ureteral bougie could the obstruction in the left ureter be passed, permitting the subsequent insertion of a ureteral catheter. The obstruction in the right ureter later disappeared spontaneously. Perhaps the obstruction in the left would similarly have disappeared had we been willing to withhold cystoscopic manipulation at the risk of death from anuria. In any case, our experience would lead us to believe that where the life of the patient is not seriously threatened, conservative measures (high fluid intake without cystoscopic manipulation) should be given adequate trial. The terms, uroliths and concretions, hardly describe accurately the putty-like appearance of the masses of crystals when seen cystoscopically. Although apparently too insoluble to be dislodged by lavage while on the table, the fact that they spontaneously dissolved and were painlessly passed in the form of sediment in the space of a few days is in marked contrast with the behavior of ordinary uroliths or concretions.

**Summary.** The case of a 13-year-old girl is reported who, following sulfapyridine therapy, recovered from influenzal meningitis but

\* Two more cases with recovery are being reported by Dr. E. L. Noone. One case of fulminating influenzal encephalo-meningitis with a positive blood culture was treated with sulfapyridine on Dr. James Kay's service in the Episcopal Hospital and died; one case treated with sulfapyridine, serum and sulfathiazole on Dr. Leonard F. Bender's service recovered.

almost succumbed to bilateral ureteral obstruction. This case emphasizes: 1, The value of sulfapyridine in the treatment of influenzal meningitis; 2, its potentialities for damage to the upper urinary tract; and 3, satisfactory recovery after complete ureteral blockage.

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## DELIRIUM TREMENS.

## A STUDY OF VARIOUS METHODS OF TREATMENT.\*

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IN 1937 a report was presented from this clinic by Piker and Cohn<sup>14</sup> on the comprehensive management of delirium tremens. This report was based on a study of 300 consecutive cases of delirium tremens from January 1, 1933, to July 1, 1935. These cases were all submitted to a routine type of therapy and a brief review of the treatment is as follows:

\* Read before the American Psychiatric Association, May 23, 1940, in Cincinnati, Ohio.

1. No alcohol is given the patient from the time that he comes under our direction.

2. Absolute bed rest is ordered in an attempt to avoid as far as possible physical strain on the heart, and to give the patient the maximum opportunity for sleep.

3. Close observation on the part of the ward personnel is insisted on, so that the patient has a minimal chance to injure himself or others.

4. Extract of cascara, 10 gr. (0.6 gm.), is given on admission, followed by 1 ounce (30 gm.) of magnesium sulphate by mouth 2 hours later.

5. Magnesium sulphate (1 ounce) is given every morning for 3 days, unless there have been more than 4 bowel movements the previous day.

6. Alkalies in the form of imperial drink (*potus imperialis*, British Pharmaceutical Codex) are given 3 times daily.

7. Spinal fluid drainage is done as soon after admission as possible, and may be repeated as often as is indicated.

8. Fifty cubic centimeters of 50% dextrose is given intravenously from 2 to 4 times a day.

9. Ten cubic centimeters of 50% magnesium sulphate is given intramuscularly 1 to 2 times a day for 2 days.

10. Caffeine sodium benzoate,  $7\frac{1}{2}$  gr. (0.5 gm.), is given hypodermically every 4 hours for 6 doses. If indicated, this procedure may be repeated.

11. The patient is digitalized in from 36 to 48 hours, and is then placed on a maintenance dose.

12. Paraldehyde (100%), 3 or 4 drams (from 11 to 15 cc.), is given from 1 to 3 times a day for sedation. Intravenous sodium amytal may be used, though we would hesitate to recommend that more than from 10 to 15 gr. (0.6 to 1 gm.) be given to any one patient. Hydrotherapy is indicated wherever possible.

13. A high caloric soft or liquid diet, supplemented by vitamin-containing substances—especially of the B group—is ordered. If the patient has difficulty in retaining nourishment, gastric lavage with a sodium bicarbonate solution should be done.

14. Fluids are given according to the patient's desires. The factor of the patient's comfort should be the determining one in governing the amount of fluids given.

15. Should the patient be asleep, he is not awakened for any reason, medicinal or otherwise.

Under this régime the mortality rate was 5.3% and the average stay in the hospital was 4.8 days.

The purpose of this paper is to review the results of treatment in 234 consecutive cases of delirium tremens admitted to the Psychiatric Pavilion of the Cincinnati General Hospital from July 1, 1935, to February 1, 1940. Cases in this group all showed the characteristic findings of delirium tremens, that is, a history of alcoholism with an acute psychosis characterized by disorientation, hallucinations, apprehension, tremors, insomnia, anorexia, and general signs of toxicity. Although cases of so-called "incipient delirium tremens" (same as delirium tremens with absence of psychotic manifestations) are treated in our clinic similarly to the full-blown delirium tremens cases, none of these are included in this study. Since the original report in 1937, we have instituted changes in treatment which will be discussed in this and subsequent reports.

**Modifications in Treatment and Their Results.** In order to evaluate the efficacy of various treatment maneuvers we have arbitrarily chosen as our basis of comparison three factors common to all cases.

1. The duration of psychotic material. We considered a patient no longer psychotic when he became oriented, stopped hallucinating, and was devoid of delusions.

2. The length of hospital stay. This was determined by complete recovery from the disease. In addition to absence of psychotic material, we used as criteria for recovery the absence or marked diminution of tremors, return of appetite, ability to sleep satisfactorily, and loss of apprehensiveness.

3. The amount of paraldehyde used in each case. We interpreted this factor as an index of the turbulency of the patient's course.

Since there were only 3 deaths in this series, we did not include the mortality rate as a factor in judging the various treatments used.

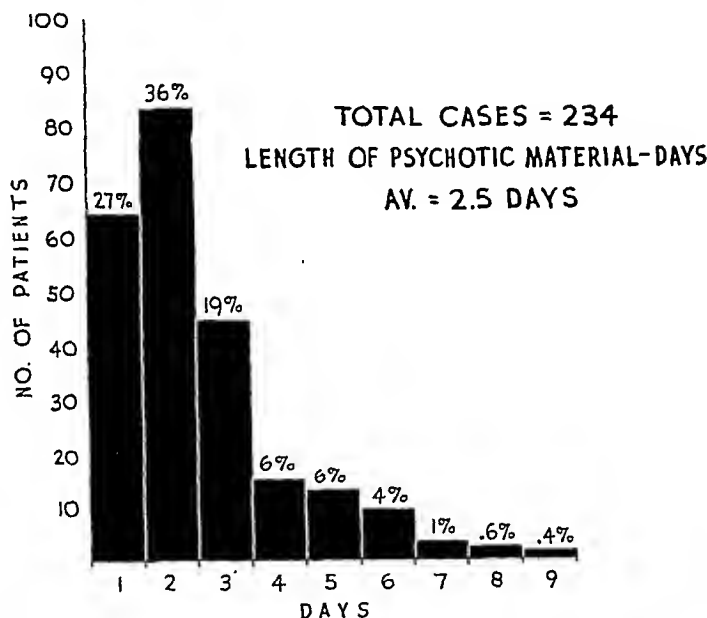


FIG. 1.—Length of psychotic material in days of 234 cases of delirium tremens regardless of type of therapy.

Figures 1 and 2 illustrate the duration of psychotic material and duration of the disease respectively for the total group of 234 cases, regardless of variations in treatment and calculated from time of admission to the hospital. The average duration of psychotic material was 2.5 days, and the average duration of the disease (hospital stay) was 5.3 days.

**Fluids.** One of the first modifications in the treatment routine was forcing fluids. Since this subject has already been discussed by Piker,<sup>13</sup> we will only present his conclusions.

Figure 3 illustrates the results in 142 cases treated with routine therapy and forced fluids (3000 to 4000 cc. daily). The average duration of illness was 4.75 days; while in a similar group of 142 cases in whom fluids were limited (under 1000 cc. daily), the average duration of illness was 4.65 days. The mortality rate was the same—8 deaths in each series.

**Digitalis.** The second modification in the treatment was the omission of digitalis. In Figure 4 it is seen that in a group of 91 cases treated with routine therapy plus digitalis, the average duration of psychotic material

was 2.1 days, as compared to 2.3 days in a group of 59 cases treated without digitalis. The average hospital stay in the digitalized group was 4.8 days, as compared to 5 days in the non-digitalized group. The average paraldehyde was 16 drams, as compared to 18 drams.

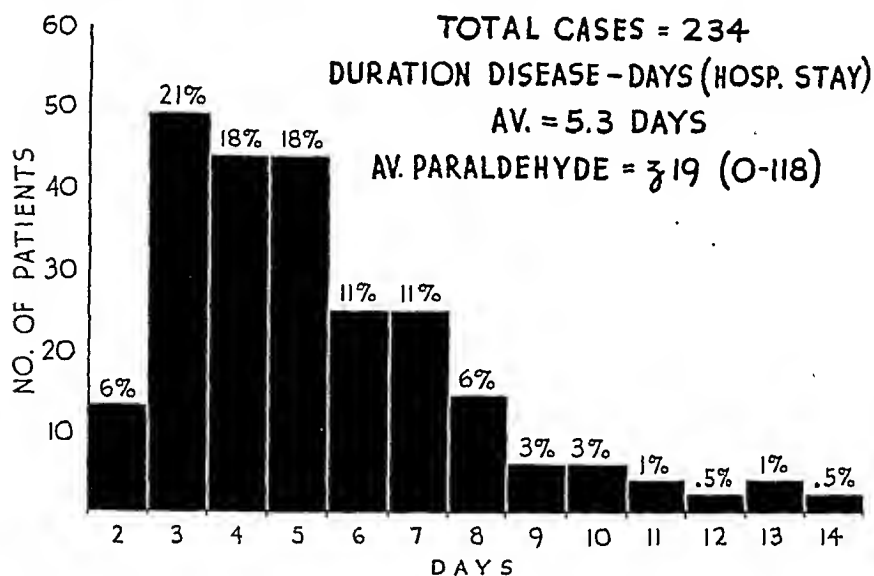


FIG. 2.—Duration of disease (hospital stay) and the average amount of paraldehyde used in 234 cases of delirium tremens regardless of type of therapy.

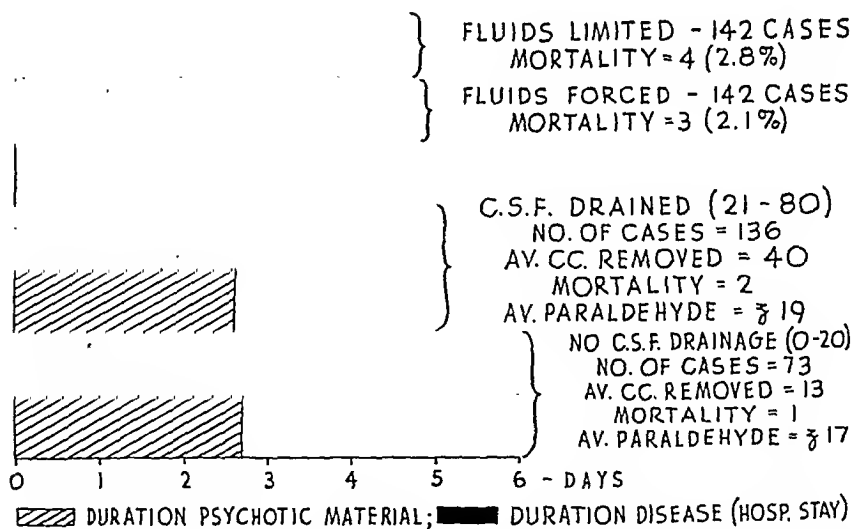


FIG. 3.—Results in 284 cases of delirium tremens treated with routine therapy in which fluids were limited (under 1000 cc.) in 142 cases (Piker and Cohn). (A comparison of results in 136 patients who had cerebrospinal fluid drainage with 73 patients who were not drained of cerebrospinal fluid. Note similarity in results in all groups.)

**Sucrose and Glucose.** The next change in treatment was the substitution of sucrose for glucose. In Figure 4 it is seen that in 86 patients treated with

routine plus glucose (the majority of these patients were digitalized), the average psychotic duration was 2.6 days as opposed to 2.5 days in 107 patients treated with routine plus sucrose (the majority of these patients were not digitalized). The average hospital stay was 5.3 days in the glucose group, as compared to 5.7 days in the sucrose group; and the average paraldehyde was 15 drams, as compared to 20 drams.

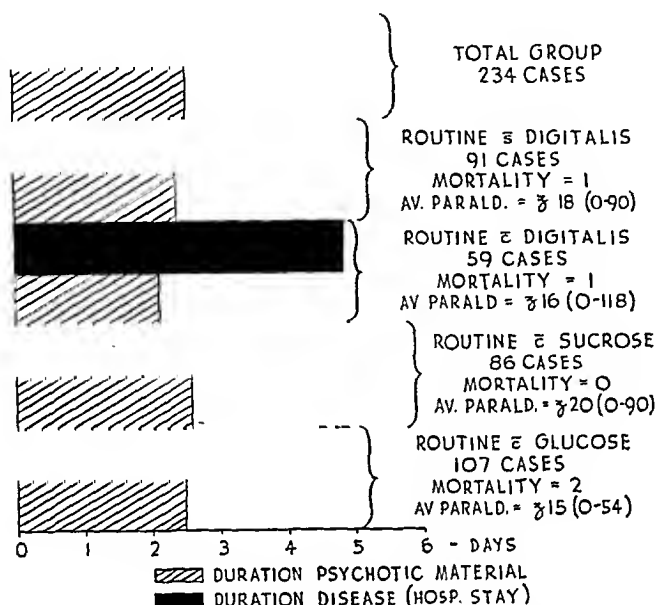


FIG. 4.—Comparison of results in patients treated with and without digitalis. (Results in patients treated with intravenous sucrose [50 cc. of 50% solution b.i.d.] as compared to patients treated with glucose [50 cc. of 50% solution b.i.d.]. Note similarity in results in all groups.)

**Cerebrospinal Fluid Drainage.** Figure 3 compares results in 136 cases in which more than 21 cc. of spinal fluid was drained at one tap, to 73 cases in which less than 21 cc. was drained. The average amount drained from the first group was 40 cc.; and the average drainage from the second group was 13 cc. The average psychotic duration for the two groups was 2.6 days and 2.7 days, the average hospital stay 5.2 days and 6 days, and the average paraldehyde used 19 drams and 17 drams.

**Vitamins.** In 1936 we treated 17 cases with liver extract parenterally. In Figure 5 it is seen that the average psychotic duration in these cases was 3.3 days, the average hospital stay 5.3 days, and the average paraldehyde was 18 drams. The introduction of refined vitamin preparations such as thiamin chloride ( $B_1$ ) and nicotinic acid led us to try these preparations. In June, 1938, we started to use nicotinic acid orally (500 to 1500 mg. daily) in addition to routine treatment; and Figure 5 illustrates the results in a group of 14 cases. The average psychotic duration was 3.2 days, the length of illness was 7 days and average paraldehyde was 38.5 drams.

In July, 1939, we began to treat alternate cases of delirium tremens with vitamin  $B_1$ \* (50 mg. daily, parenterally), paraldehyde, and a diagnostic lumbar puncture. Figure 5 illustrates the results. The average psychotic duration of the  $B_1$  group was 2.2 days, as compared to 2 days in the control

\* Vitamin  $B_1$  supplied through the courtesy of the Wm. S. Merrell Chemical Company, Cincinnati, Ohio.

group; the hospital stays were 6.6 days and 5.5 days; and the average amounts of paraldehyde used were 11.3 drams and 15 drams.

*Miscellaneous.* In addition to the above we have a small number of cases given sodium chloride with the routine treatment, and 4 cases treated only with insulin covered by glucose. These groups are too small for evaluation; but an interesting fact is that 3 of the 4 insulin-treated cases required no sedation.

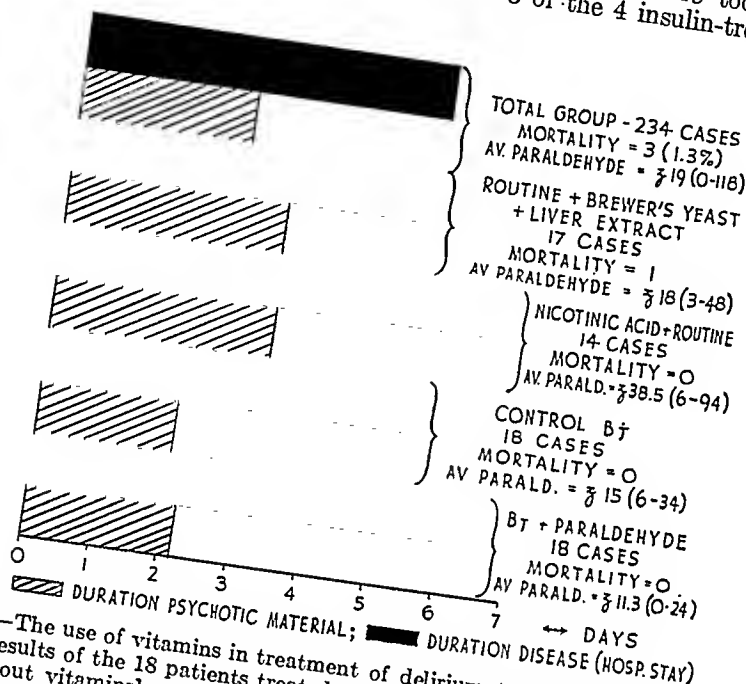


FIG. 5.—The use of vitamins in treatment of delirium tremens. (Note the similarity in results of the 18 patients treated with B<sub>1</sub> to the 18 controls [routine treatment without vitamins]. Also the increase in duration of psychotic material and hospital stay in the nicotinic acid group.)

**Discussion.** We would agree with Bowman<sup>1</sup> and his workers that although a good deal is known about delirium tremens from the clinical aspect, little is known as to the exact etiology. We emphasize that our treatment is purely symptomatic, except in those cases treated with only vitamin B<sub>1</sub> and paraldehyde in an attempt to evaluate the factor of B<sub>1</sub> deficiency.

**Fluids.** Piker<sup>13</sup> has already shown that there was no difference in the outcome of his cases regardless of whether fluids were forced or limited. Originally we limited fluids to counteract the cerebral edema and the supposed increased intracranial pressure in these cases; but since it has been felt that the general toxic factors were more important, we have been forcing fluids as part of our routine.

**Digitalis.** In our series, there is not much difference in results in patients treated with or without digitalis. The drug was originally used to prevent cardiac failure, as it was noted that most cases coming to autopsy have two characteristic diagnoses: cerebral edema ("wet brain") and toxic myocarditis with acute dilatation. It was thought that the drug might prevent the latter. However,

we no longer use digitalis in our treatment, because as already noted, patients recover as quickly without it as with it; and inasmuch as delirium tremens in itself involves considerable toxicity, it appears rational to eliminate any toxic drug such as digitalis. There is a general agreement among cardiologists and internists that digitalis is probably contraindicated in toxic states of all sorts.<sup>4,17</sup> Furthermore, we have noted no decrease in the tachycardia of this disease with digitalis.

*Sucrose and Glucose.* In 1934 and after there were reports in the literature<sup>2,3,7,8,11</sup> to the effect that sucrose was a better agent for reducing intracranial pressure than glucose. Sucrose tended to keep the pressure down for longer periods, and prevented the development of a late rise in cerebrospinal fluid pressure. Since one aim of our therapy was to reduce increased intracranial pressure and cerebral edema, we started to use sucrose intravenously (50 cc. of a 50% solution B.I.D.).

At this point it may be appropriate to say a few words about this subject of cerebral edema ("wet brain") and increased cerebrospinal fluid pressure in delirium tremens. There has been a good deal of speculation about cerebral edema and increased cerebrospinal fluid pressure in this disease mainly due to one fact: that in patients dying with delirium tremens the most consistent cerebral finding is that of cerebral edema. To our knowledge, no conclusive work has been done on this subject, although it has been shown by Rosenbaum, Herren, and Merritt<sup>16</sup> that only 25% of acute alcoholics (including delirium tremens cases) have increased intracranial pressure (180 mm. and above), and it has also been noted by Rosenbaum and Merritt<sup>16</sup> that in 38 cases of acute Korsakoff psychosis, only 16% show increased pressure (180 mm. and above). About 25% of our cases showed increased pressure (180 mm. and above). (This subject will be discussed in detail in another report.)

It suffices to say at the present that although it appears that the majority of patients with delirium tremens have normal pressure, there is no proven causal relationship between cerebral edema and cerebrospinal fluid pressure. Therefore, we used sucrose and glucose to combat cerebral edema even in the face of normal cerebrospinal fluid pressure. Our results show little difference insofar as the two solutions are concerned. It is likely, however, that carbohydrate metabolism is disturbed in this disease; and attempts should be made to correct this. Sucrose injected intravenously is not utilized in carbohydrate metabolism.<sup>2,3,7,8,11</sup> Moreover, it is established that a high percentage of glucose injected intravenously in strongly hypertonic solutions is excreted in the urine,<sup>18</sup> with only a small fraction being utilized in carbohydrate metabolism. Consequently, we believe that the most rational approach to this problem would be the administration of hypertonic sucrose to combat cerebral edema (and increased cerebrospinal fluid pressure when



present), and the use of carbohydrates by mouth, or in 5% to 10% solution by slow intravenous injection if the oral route is not feasible.

*Cerebrospinal Fluid Drainage.* Until about a year ago most patients were drained of spinal fluid in an attempt to alleviate cerebral edema. In the past year only diagnostic taps were done. Since there were only 28 cases who had less than 10 cc. taken off at one tap, we included 45 cases from whom between 11 and 20 cc. had been drained to make a total of 73 cases in what we considered the "non-drainage" group. As already noted, there is no difference in results in these groups. At present, our policy is to reduce the pressure by half if increased; and if not increased, to remove enough for routine spinal fluid examination.

*Nutrition.* In the last several years the whole concept of alcoholism, especially regarding pathologic effects on the nervous system, has been subject to a new point of view, namely the rôle of vitamin deficiency in these cases. It has long been known that the alcoholic eats little; or, if he eats, that he utilizes inadequate amounts of the ingested food. Spies and De Wolf,<sup>19</sup> Strauss,<sup>21</sup> Wechsler,<sup>22</sup> Goodhart and Jolliffe,<sup>6</sup> and many others have suggested that the main effect of alcohol on the nervous system was not caused by the alcohol itself, but by the vitamin deficiency connected with the alcoholism. Most of this work has been done on so-called alcoholic peripheral neuritis. Inasmuch as the alcoholic who develops delirium tremens is a notoriously poor eater, and furthermore usually shows gastro-intestinal symptoms before and during delirium tremens, we felt we should attack this deficiency by the addition of vitamins of the B group.

Only 17 cases were treated with liver extract (10 cc., deep injection daily). These patients did no better than the routine group; and as a matter of fact had a longer duration of psychotic material, namely 3.3 days.

We first used nicotinic acid in addition to our routine therapy in June, 1938, after it had been shown by Spies and his workers<sup>20</sup> that this vitamin was specific in the acute psychosis of pellagra. Maizner and Krause<sup>10</sup> reported the use of nicotinic acid with good results in 1 case of delirium tremens. The 14 cases we treated with nicotinic acid had an average psychotic duration of 3.2 days, which is almost a day longer than the group treated without any vitamin; and they also required an average of 38.5 drams of paraldehyde, which is about twice as much as the non-vitaminized group needed. This seems to suggest that the addition of nicotinic acid prolongs the illness, if it does anything. As already stated, one aim in treatment is to relieve cerebral edema and increased cerebrospinal fluid pressure when present. Moore<sup>12</sup> has shown that nicotinic acid causes dilation of the cerebral blood-vessels; and it has also been demonstrated by Ferris, Rosenbaum, Roseman, and Brower<sup>5</sup> that nicotinic acid increases the rate of cerebral circulation and raises

intracranial pressure. It is perhaps these factors which tend to aggravate and make for cerebral edema that account for the increase in duration of psychotic material in these patients. We believe that nicotinic acid is not warranted in treatment unless a specific nicotinic acid deficiency exists in the patient.

Recently there has been a great deal of interest in the use of thiamin chloride (vitamin B<sub>1</sub>) in all sorts of psychiatric, neurologic, and medical conditions. There have been several reports of its use in delirium tremens, mainly in the foreign literature. Kloster<sup>9</sup> treated 10 patients with this drug; and though he realized this was too small a group for true evaluation, he did notice that the patients slept well with the drug. Since July, 1939, we have treated alternate cases with B<sub>1</sub> (50 mg. daily) and paraldehyde; and although this work is still in progress, we feel justified in making a preliminary report of 18 cases, with 18 controls treated routinely. As was noted earlier there was not much difference in the course of the two groups, except the group treated with B<sub>1</sub> required not only less paraldehyde than the controls, but less than any other group in our entire series. This finding is consistent with the supposed sedative action of B<sub>1</sub>. Two patients in this group required no paraldehyde at all. However, what is more interesting and striking is that 2 patients came in with incipient delirium tremens, received B<sub>1</sub> (50 mg. daily) from the time of admission, and developed typical delirium tremens after being in the hospital 2 days. These observations lead to the question of whether a B<sub>1</sub> or nicotinic acid deficiency plays any part in the production of this syndrome. From our experience so far all we can conclude is that once the disease starts, the addition of B<sub>1</sub>, nicotinic acid, liver extract, and Brewer's yeast do not seem to aid in shortening the illness. This brings up the following question: Is the vitamin or nutritional deficiency an important precipitating factor, even though vitamin treatment does not influence the illness once it starts? One way to approach this problem would be to allow an alcoholic to drink all he wants, but to make certain his vitamin intake during his drinking period has been adequate, that is, along the lines adopted by Spies and De Wolf<sup>19</sup> and Strauss<sup>21</sup> in their study of alcoholic pellagra and alcoholic neuritis.

TABLE 1.—SUMMARY OF THE ROUTINE TREATMENT OF DELIRIUM TREMENS FROM PIKER AND COHN.

<i>Principles.</i>	<i>Methods.</i>
Safeguarding the patient	{ Hospitalization Adquate observation
Prevention of exhaustion	{ Circulatory support (digitalis, caffeine, glucose) Sedation (paraldehyde, spinal fluid drainage, caffeine, glucose, MgSO <sub>4</sub> )
Promotion of elimination	{ Bowel (cascara, MgSO <sub>4</sub> ) Kidney (caffeine, glucose, digitalis)
Decrease of cerebral edema	{ Spinal fluid drainage Glucose, MgSO <sub>4</sub> , caffeine
Promotion of nutrition	{ Readily digestible, high caloric, high vitamin diet For severe gastritis, lavage

We have attempted to answer the question by doing just this, and at this time would like to mention the experiment. A chronic alcoholic who was admitted to the Psychiatric Service four times during the past year with delirium tremens volunteered for the study after fully recovering from his last episode. He consumed  $12\frac{1}{2}$  quarts of whiskey (90 proof) in 14 days; and each day he received 50 mg. B<sub>1</sub> (parenterally) and 500 mg. nicotinic acid (orally). He ate practically nothing during the experiment, although he consumed large quantities of milk daily, using it as a chaser. On the thirteenth day of his drinking he developed delirium tremens. We realize that this is only 1 case; but it seems safe to assume that in this 1 case the delirium tremens was not on the basis of a B<sub>1</sub> or nicotinic acid deficiency.

TABLE 2.—ANALYSIS OF MORTALITY FIGURES IN 534 CASES OF DELIRIUM TREMENS.

<i>Mortality Figures.</i>	
July 1, 1935 to February 1, 1940:	
234 cases—Total deaths . . . . .	3 (1.3%)
Uncomplicated deaths . . . . .	2 (0.9%)
<i>Severe Complications.</i>	
Lobular pneumonia and acute renal insufficiency . . . . .	1
January 1, 1933 to July 1, 1935:	
300 cases—Total deaths . . . . .	16 (5.3%)
Uncomplicated deaths . . . . .	7 (2.3%)
9 severe complications:	
Suppurative parotitis and bronchopneumonia . . . . .	1
Severe gastric hemorrhage and lobar pneumonia . . . . .	1
Heat stroke . . . . .	2
Lobar pneumonia . . . . .	3
Severe bronchopneumonia . . . . .	1
Severe stab wounds of chest and abdomen . . . . .	1
Combined mortality, 534 cases:	
Total deaths . . . . .	3.5%
Uncomplicated deaths . . . . .	1.7%

*Deaths* (Table 2). Though the number of deaths in our series was too small to permit the use of mortality figures as an index of the comparative values of the treatment variations we have discussed, it would be well to review these figures. In the 234 cases with which this paper is chiefly concerned, there were 3 deaths, a mortality rate of 1.3%. Comparing this rate with the one of 5.3% reported by Piker and Cohn from this clinic would seem to present an appreciable discrepancy. The explanation for this discrepancy is as follows: previous to July 1, 1935, all patients with delirium tremens (regardless of type or severity of coincidental complicating disease) were treated on the Psychiatric Service. As a result, the 16 deaths occurring in the series of 300 cases reported by Piker and Cohn included 9 whose conditions were primarily medical or surgical, whose delirium tremens was secondary, and whose deaths should most properly be ascribed to changes not associated with delirium tremens. These 9 cases included 1 suppurative parotitis and bronchopneumonia, 1 severe gastric hemorrhage and lobar pneu-

monia, 2 heat strokes, 3 lobar pneumonias, 1 severe bronchopneumonia, and 1 case of severe stab wounds of the chest and abdomen. If these cases are deleted from the series, the mortality rate becomes 2.4%. Similarly, the 3 deaths in the more recent group included 1 patient who had severe lobular pneumonia, and who was transferred to the Medical Service and died there. With this case omitted, the mortality rate for the more recent series becomes 0.9%.

Combining the two groups, and including only those patients who had either complications of secondary importance or none at all, the mortality rate for 524 consecutive cases of delirium tremens treated variously in our clinic becomes 1.7%.

**Conclusions.** A total series of 524 consecutive cases of delirium tremens was treated in the Psychiatric Division of the Cincinnati General Hospital from January 1, 1933, to February 1, 1940. Several different treatment maneuvers were attempted with several subgroups of this series, with the variation in results being for the most part insignificant.

The similarity in results, regardless of type of therapy used, suggests that the treatments be examined for factors common to all of them. Insofar as we have been able to discover, these common factors included only hospitalization, paraldehyde, lumbar puncture (some for drainage and some for diagnostic purposes), and the attitude toward these patients on the part of the department personnel. Of these factors, our attitude seems to us perhaps particularly significant. Delirium tremens has been for several years the chief research problem of the department. As a result much time is given to delirium tremens patients, with the interest of the research clinicians permeating everyone involved in the management of these cases. The *esprit de corps* that has developed in this connection is apparent in the general reaction of personal defeat on the part of the entire personnel when 1 of these patients dies.

A consideration of this attitude has led us to speculate regarding the value of "superficial" psychotherapy (much attention, reassurance, and our own feeling of confidence growing out of our low mortality rate) in delirium tremens. It is of interest in this regard that numerous repeaters return to our wards of their own accord when they begin to feel "jittery." Furthermore, we find it difficult to ignore the fact that 2 patients relaxed into satisfactory sleep after being given placebos. And finally, our results seem to us to indicate strongly that regardless of what sort of treatment procedure is used, and so long as no measures are instituted which are actually injurious, adequate general medical and psychiatric care should serve to keep the mortality rate in uncomplicated delirium tremens down to a minimum.

We have been unable to find, thus far, a specific therapeutic medicinal procedure for delirium tremens. It is our feeling that

the place of psychotherapy in the treatment of this disease merits more consideration generally than it has received until now.

In the light of our low mortality figures, it seems to us that the problem in delirium tremens at this time is not so much one of discovering the proper method of therapy as it is an elucidation of the etiologic factors involved.

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## THE PRODUCTION OF FATTY AND FIBROTIC LIVERS IN GUINEA PIGS AND RABBITS BY SEEMINGLY ADEQUATE DIETS.\*

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FATTY livers have been produced in experimental animals in various ways. These methods involve the use of a toxic agent (carbon tetrachloride,<sup>4</sup> chloroform,<sup>8</sup> or phosphorus,<sup>12</sup> surgical extirpation of organs such as pancreatectomy,<sup>3</sup> removal of 65% of liver,<sup>12</sup> or use of a grossly unbalanced diet deficient in protein and overabundant in fat.<sup>1,2,11</sup> In 1939, we<sup>20</sup> reported the production of fatty livers in the guinea pig by means of a diet which appears to be well balanced but devoid of vitamin C. Our work at that stage suggested that the absence of vitamin C was not wholly responsible for this pathologic change. In the present study we have extended

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these observations and investigated the relationship of other substances to this type of experimentally produced liver damage.

**Fatty Livers Produced by Scorbutogetic Diet** (Table 1). The diet we used was essentially the scorbutogetic diet originated in 1922 by Sherman *et al.*,<sup>18</sup> except that whole milk powder was used instead of skimmed milk powder. This diet we shall refer to as Diet 1 (Table 5). A group of guinea pigs were put on this diet and were given an abundance of ascorbic acid. This was administered by means of a syringe by mouth, as an aqueous solution. This supplement was withdrawn after about 3 weeks and the animals were allowed to die from scurvy. Another group of animals were given subminimal doses of ascorbic acid to prolong their survival (Table 1).

TABLE 1.—EFFECT OF SCORBUTOGETIC DIETS ON LIVER FAT.

Serial No. of animal.	Diet.		Vitamin C.		% liver of body weight.	Mg. lipids per 1 gm. liver tissue.
	Type.	No. of days.	Amount.	No. of days.		
SIM 3	Starved	11	Abund.	..	4.1	13.6
NM 1	Normal	..	Abund.	..	...	21.2
NM 2	Normal	..	Abund.	..	5.3	24.0
NM 3	Normal	..	Abund.	..	...	19.9
IM 1	1	47	Free	25	10.5	238.8
IM 2	1	50	Free	28	9.3	260.9
IM 4	1	49	Free	27	8.0	109.3
IM 5	1	50	Free	28	7.7	117.9
IM 6	1	52	Free	30	6.9	122.1
HM 1	1	54	Low	54	8.6	207.0
HM 2	1	33	Low	33	...	130.7
HF 3	1	53	Low	53	4.7	63.7
HF 4	1	67	Low	67	5.06	91.5
HF 1	1	117	Low	117	6.8	300.6
GM 2	2	46	Free	21	7.5	116.6
GF 3	2	46	Free	21	6.9	104.5
GF 4	2	48	Free	6	6.8	78.5
GM 4	2	49	Free	7	6.6	125.0
GF 5	2	58	Free	17	7.5	110.3
GF 6	2	55	Free	14	6.03	39.1

All animals were autopsied, and organs showing noteworthy gross changes were taken for microscopic examination. Sections of liver tissue were stained by eosin and hematoxylin and Sudan 3. A total of about 0.5 gm. of tissue was taken from the various lobes of the liver to obtain an average sample. This was analyzed for total lipids by the micro-method of Van Slyke.<sup>10</sup> The livers of the animals that were completely deprived of vitamin C showed a lipid content of 10.9% to 26%, while those on the subminimal amounts of vitamin C and dying from chronic scurvy had liver fat content of 6.3% to 30%, depending roughly on the length of time they survived (Table 1).

**Effects of Yeast and Dextrose on Liver Fat** (Table 1). Since dextrose has been thought to have a favorable effect on various types of liver injury, we modified the above diet by replacing part

of the bran and oats with 10% dextrose. The 1% desiccated brewer's yeast was added to neutralize the loss of the B complex created by the removal of 11% of bran and oats (Table 5) (Diet 2). A group of 6 guinea pigs were put on this diet and allowed to die from scurvy. The livers of these animals contained 3.9% to 12.5% of fat, which is considerably less than the amount present in the livers of animals on Diet 1. This apparently favorable effect of dextrose and yeast is refuted in the following experiment.

**Effect of Ascorbic Acid and Orange Juice on Liver Fat (Table 2).** Four groups of guinea pigs were used (Table 2). Group 1 was fed on Diet 1 supplemented by an abundance of pure ascorbic acid. Group 2 was also on Diet 1 but received orange juice as the anti-scorbutic agent. Groups 3 and 4 were fed Diet 2, supplemented with crystalline ascorbic acid and orange juice respectively.

TABLE 2.—INFLUENCE OF YEAST, ORANGE JUICE, AND CRYSTALLINE ASCORBIC ACID ON LIVER FAT.

Serial No. of animal.	Diet.		Vitamin C.	% of liver of body weight.	Mg. lipids per 1 gm. liver tissue.
	Type.	No. of days.			
1 EM 2 . . . . .	1	46	Cryst.	7.1	129.2
1 EF 5 . . . . .	1	67	"	7.04	136.6
1 EF 3 . . . . .	1	74	"	8.8	302.4
1 EM 4 . . . . .	1	142	"	7.2	319.2
1 EF 8 . . . . .	1	42	O. J.	4.1	38.3
1 EF 9 . . . . .	1	42	"	7.7	105.1
1 EF 7 . . . . .	1	62	"	7.3	142.3
1 EF 6 . . . . .	1	173	"	...	194.3
EF 2 . . . . .	2	100	Cryst.	4.8	74.8
EM 1 . . . . .	2	154	"	11.3	238.4
2 EM 3 . . . . .	2	34	"	7.3	110.5
2 EM 1 . . . . .	2	58	"	7.1	122.7
2 EM 2 . . . . .	2	92	"	8.99	326.9
2 EF 4 . . . . .	2	157	"	9.3	342.0
2 EM 5 . . . . .	2	63	O. J.	3.5	248.4
2 EM 6 . . . . .	2	341	"	4.5	125.7
2 EM 7 . . . . .	2	217	"	5.9	222.7
2 EM 8 . . . . .	2	213	"	9.3	340.2

It will be noted that the group receiving the orange juice with Diet 1 had a lower liver fat content than those on this diet with the ascorbic acid. Thus the group on the pure ascorbic acid had a liver lipid content of 12.9% to 31.9%, as compared with 3.8% to 19.4% of fat in the group on Diet 1, supplemented with the orange juice. There is no difference in longevity between these two groups. Therefore, a slight favorable effect on the liver lipids is noted in this experiment by using orange juice as the antiscorbutic factor. However, the two groups of animals on Diet 2 do not show this favorable effect of orange juice. Thus the group supplemented with orange juice have a liver lipid content of 12.5% to 34% and the group supplemented with pure ascorbic acid gives figures of 7.5% to 34%. However, the interesting thing in the group on the enriched Diet 2 supplemented with orange juice is their longevity. Only 1 animal

died after 63 days, 2 died after 200 days and 1 was sacrificed after 11 months. Apparently, the diet enriched with yeast and dextrose and supplemented with orange juice tends to keep the animals in an improved state of health and thus overcomes the deleterious effect of the fatty liver for a longer period of time. There seems to be a rough proportion between the survival time and the amount of fat in the liver. That is, the longer the animal survives on this diet the more fat will be deposited in the liver. There is one conspicuous exception to this apparent relationship. Animal 2 EM 6 (Table 2) was sacrificed after 300 days and the liver lipids were only 12.5%. However, this animal did not die spontaneously and this may have something to do with the relatively low fat content.

**Effect of Lipocaic\* and Choline on Liver Fat** (Table 3). Because of the known lipotropic effect of choline<sup>1-3,5,11</sup> and the lipotropic effect obtained by Dragstedt<sup>6,7,15</sup> and his co-workers with a pancreatic extract (lipocaic), we used these substances in a group of experiments. We repeated the experiment of Table 1. That is, we permitted the animals to die of scurvy on Diet 1 but administered daily to each animal of a group 20 mg. of choline; and to each animal of another group, 475 mg. of lipocaic. These substances were dissolved in water and administered by mouth with a syringe.

TABLE 3.—INFLUENCE OF LIPOCAIC AND CHOLINE ON LIVER FAT.

Serial No. of animal.	No. of days on Diet 1.	No. of days Vitamin C-free.	% liver of body weight.	Mg. lipids per 1 gm. liver tissue.
<i>Controls.</i>				
IM 1 . . . . .	47	25	10.5	238.8
IM 2 . . . . .	50	28	9.3	260.9
IM 4 . . . . .	49	27	8.0	109.3
IM 5 . . . . .	50	28	7.7	117.9
IM 6 . . . . .	52	30	6.9	122.1
<i>Lipocaic.</i>				
1 LM 1 . . . . .	54	21	5.05	106.8
1 LM 2 . . . . .	55	22	6.4	108.1
1 LM 3 . . . . .	61	28	6.7	223.0
1 LF 4 . . . . .	48	15	8.3	128.3
1 LM 5 . . . . .	51	18	5.7	91.8
<i>Choline.</i>				
1 CM 1 . . . . .	70	20	7.6	107.6
1 CM 2 . . . . .	66	16	7.1	127.8
1 CM 3 . . . . .	72	22	7.1	196.0
1 CF 4 . . . . .	39	39	...	42.8
1 CF 5 . . . . .	70	20	6.1	67.4

The influence of lipocaic on the deposition of fat in the liver of our animals was practically negative. The animals receiving lipocaic had total liver lipids varying from 9.1% to 22.3%, while the controls varied from 10.9% to 26%. This slight decrease can certainly

\* The lipocaic used in these experiments was obtained through the courtesy of Eli Lilly & Co., for which we wish to express our gratitude.



be of no significance. With the choline supplement the results were somewhat lower; that is, from 6.7% to 19.6%, if we leave out 1 animal with a liver lipid of only 4.2% which died only 39 days after the experiment was begun. The other 4 animals were on the experiment longer than the controls or those on lipocaic and would be expected to have more fatty livers. So it appears that the choline may have a slight but certainly not spectacular effect on reducing the liver lipids in these animals.

**Effects of This Diet on Other Species of Animals.** Diet 1 has also been used by us on rabbits and rats. The rabbits like the guinea pigs acquired pathologic changes in the liver after being on the diet for some time. While increased fat in the liver was one of the findings, the tendency toward increasing fibrosis was more striking in this species. It will be noted (Table 4) that RM 2 was sacrificed after 148 days on this diet and had 24% of fat in the liver. RM 4 and RM 5 survived longer but had less fat in the liver, namely 5.3% and 9.8% respectively. It is likely that the fibrous tissue begins to replace the lipids as the pathologic process progresses. All the rabbits except the 2 that survived only 21 and 24 days had significant increase of fibrous tissue; 1 of these (RM 5) had a nodular liver which will be described below.

TABLE 4.—INFLUENCE OF DIET ON THE DEPOSITION OF FAT IN THE LIVERS OF RABBITS.

Serial No. of animal.	Diet.		% of liver of body weight.	Mg. lipids per 1 gm. liver tissue.
	Type.	No. of days.		
RN 1 . . . . .	Normal	...	..	11.7
RM 2 . . . . .	1*	24	4.0	13.9
RF 1 . . . . .	1	148	4.6	240.6
RM 3 . . . . .	1	21	3.04	22.3
RM 4 . . . . .	1	160	4.38	53.1
RM 5 . . . . .	1	281	4.05	97.9

\* The diet in the rabbits was not supplemented by ascorbic acid. This species synthesizes vitamin C.

Albino rats do not appear to get fatty livers or develop fibrous tissue in the liver on this diet. None of the rats that died on this diet showed any significant liver changes, although some of these survived over 5 months.

**Pathologic Picture.** Grossly, the fatty livers in the guinea pigs were increased in size, extending down to the mid-abdomen, and were soft in consistency. The percentage of the liver to the total body weight in the normal and fasting animals was 4% to 5%; in animals with fatty livers, it was as high as 11.3%. The organ was yellow throughout with brownish punctate areas of the vascular channels. In the livers with less fat, the yellow areas alternated with pale reddish-brown areas more closely approximating normal liver tissue. It is interesting to note that in some of these animals, in spite of a loss of 30% to 40% of their body weight and the dis-

appearance of the normal fat depots, the liver contained an excessive amount of fat. For example, 1 animal on Diet 1, dying from scurvy, lost 41% of its body weight and yet the liver had nearly 24% of fat. This is of further importance since, as has been pointed out by Wells,<sup>21</sup> the production of fatty changes in the liver and other organs by poisons is interfered with by emaciation of the animal.

TABLE 5.—DIET 1.

		Parts by weight in gm.
Rolled oats	} $\frac{1}{2}$ and $\frac{1}{2}$ by volume . . . . .	59
Wheat bran		
Powdered milk, dried	. . . . .	30
Butter fat, melted	. . . . .	8
Cod-liver oil	. . . . .	2
NaCl	. . . . .	1

DIET 2.

Rolled oats	} $\frac{1}{2}$ and $\frac{1}{2}$ by volume . . . . .	48
Wheat bran		
Powdered milk, dried	. . . . .	30
Butter fat, melted	. . . . .	8
Cod-liver oil	. . . . .	2
Dextrose	. . . . .	10
Desiccated Brewer's yeast	. . . . .	1
NaCl	. . . . .	1

Microscopically, the parenchymatous cells of entire lobules were seen to be filled with fat globules (Figs. 1 and 2). With the Sudan 3 stain, the tissue was almost a solid orange color. In the severe cases the cytoplasm of nearly all the cells consisted of one or several globules of fat with the nucleus pushed over to one side, dark staining and pyknotic. In other cells the fat globules were more finely divided but clearly visible under higher magnification. The fatty replacement was usually more severe at the periphery of the lobule. In many of the animals surviving for a long period, a creeping in of fibrous tissue into the lobule was noted (Fig. 1). The histology of the liver in the various groups of animals varied only quantitatively, depending upon the amount of fat present. In 1 guinea pig (EM 2, Table 2) the liver was large (11.3% of the body weight), firm, and finely nodular. The abdominal wall was edematous and 25 cc. of ascitic fluid was present in the peritoneal cavity. Microscopically, in addition to liver cells filled with fat, there was a conspicuous increase in fibrous tissue as demonstrated by the Mallory stain (Fig. 3). The fibrosis was especially evident around the portal radicals. Here and there, there were islets of regenerating hepatic cells. It would seem justifiable to conclude that this guinea pig had developed a cirrhosis.

The most frequent other pathologic finding and one that was probably the most frequent immediate cause of death in the animals not dying from scurvy was patchy pneumonia, sometimes lobar in distribution. Ulcerative lesions of the stomach were also noted;

these were usually multiple, and most commonly located on the greater curvature.

In the rabbits in addition to the fatty changes in the liver, there was an increase in the interlobular connective tissue. In 1 rabbit (RM 5) the liver was grossly nodular and hard (Fig. 4). The liver was cut with difficulty and emitted a grating sound. Microscopically, the organ shows pseudolobulation, the normal liver architecture having been obliterated. The pseudolobules are bounded by thick bands of connective tissue. The connective tissue also proliferated between individual liver cords. The cytoplasm of the liver cells appears highly granular and the nuclei pyknotic (Fig. 5). This animal was sacrificed after 9 months. It seems likely that had this animal been allowed to continue living, the process would have progressed to ascites and other evidence of hepatic cirrhosis. In the rabbits, the percentage of the liver to body weight was not as markedly increased as in the guinea pigs.

**Discussion.** The development of liver changes in an animal receiving an "adequate" diet leads one to wonder whether our conception of such a diet is not an erroneous one. The diets we used contain an abundance of carbohydrates in the oats and wheat bran and the pure dextrose in Diet 2. A sufficient amount of complete protein is available in the casein of the powdered milk and in the oats. Although the fat is about 20% of the diet, it is only one-half as much as in the diet of Best and others,<sup>1,2,11</sup> who produced fatty livers in the rats by dietary means. Also the protein of their diets was about 5%, while the protein in our diets was nearly 25%. As was mentioned before, the rats on our diet did not develop fatty livers. An abundance of vitamins A and D is assured by the butter fat and cod-liver oil. The B complex is found in the cereal, and in Diet 2 is supplemented with yeast. Vitamin E is present in appreciable amounts in the wheat and oats and to a lesser extent in the butter fat. Hence the addition of ascorbic acid makes this an "adequate" diet from our present conceptions. However, since no toxins were introduced to damage the liver, we can only conclude that the diet was the sole responsible factor for this pathologic change. The possibility suggests itself that some little understood or unknown factor is absent from this artificial diet and may be present in the "normal" diet of the animal which contains leafy

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#### LEGENDS FOR FIGS. 1, 2 AND 3.

FIG. 1.—Liver lobule showing large globules of fat in the parenchymal cells. The fat globules increase in size toward the periphery of the lobule. Arrows point to fibrous tissue invasion. Guinea pig IM1 (24% fat). (H. and E.,  $\times 100$ .)

FIG. 2.—Fatty liver (H. P., mag.  $\times 450$ ) stained with Sudan III, which appears gray here.

FIG. 3.—Cirrhosis of the liver in guinea pig EM1. Note the large amount of fibrous tissue (arrows), fat, and regenerating liver cells in lower right corner. (Mallory stain,  $\times 200$ .)

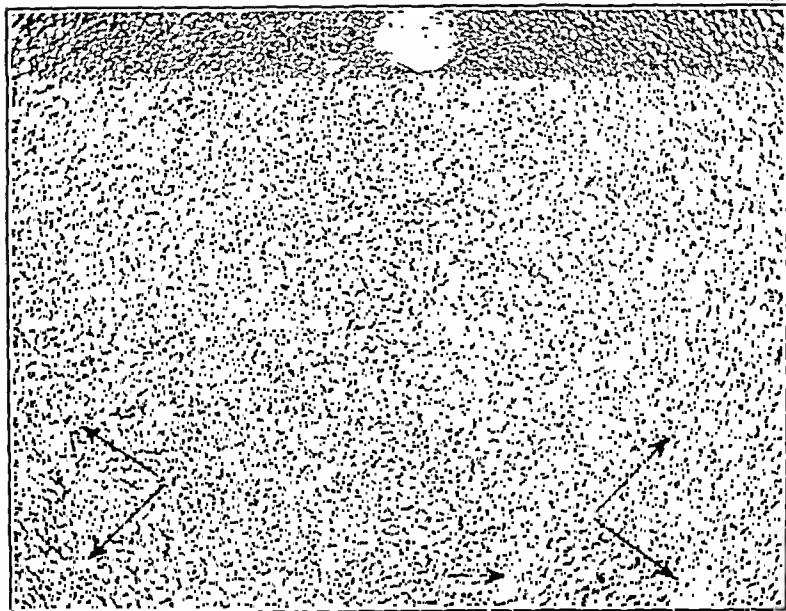


FIG. 1

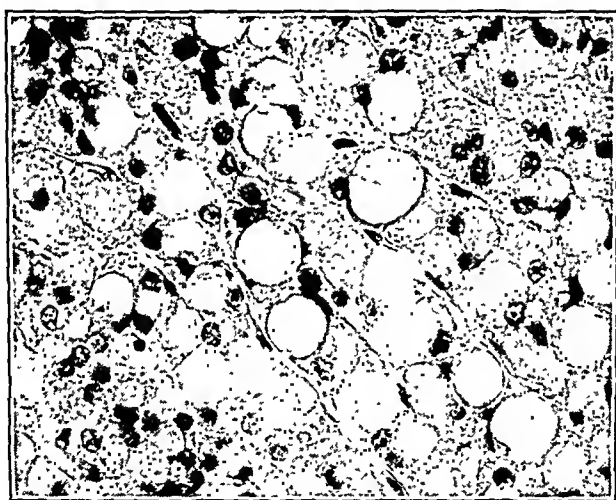


FIG. 2

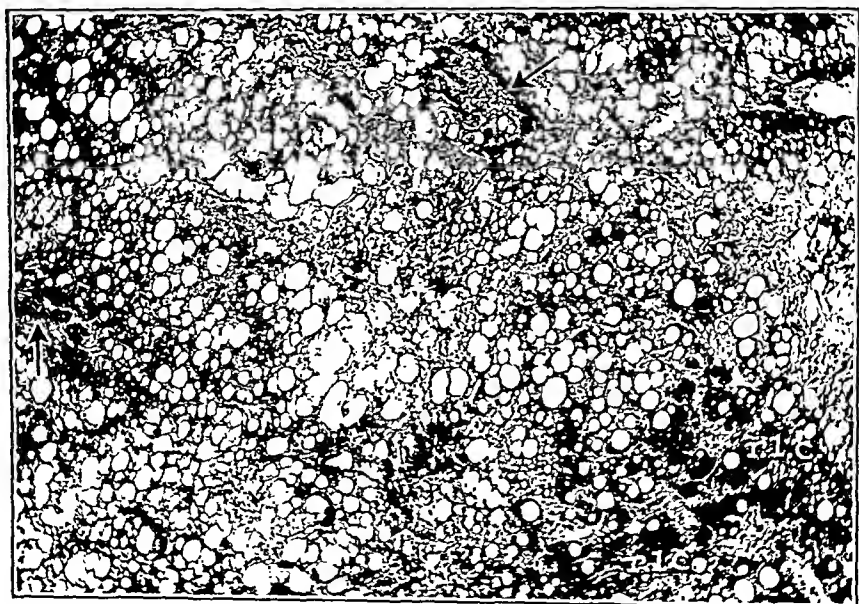


FIG. 3

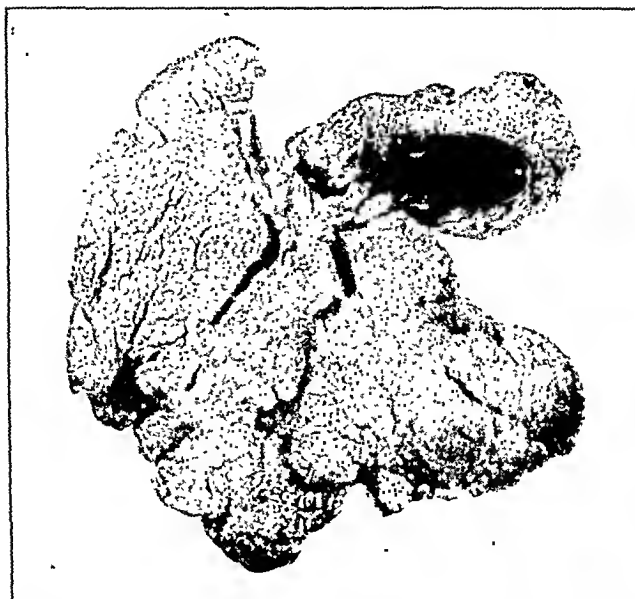


FIG. 4.—Cirrhotic liver of rabbit (RM5). Note the nodules, especially at lower edge, and the irregular surface.

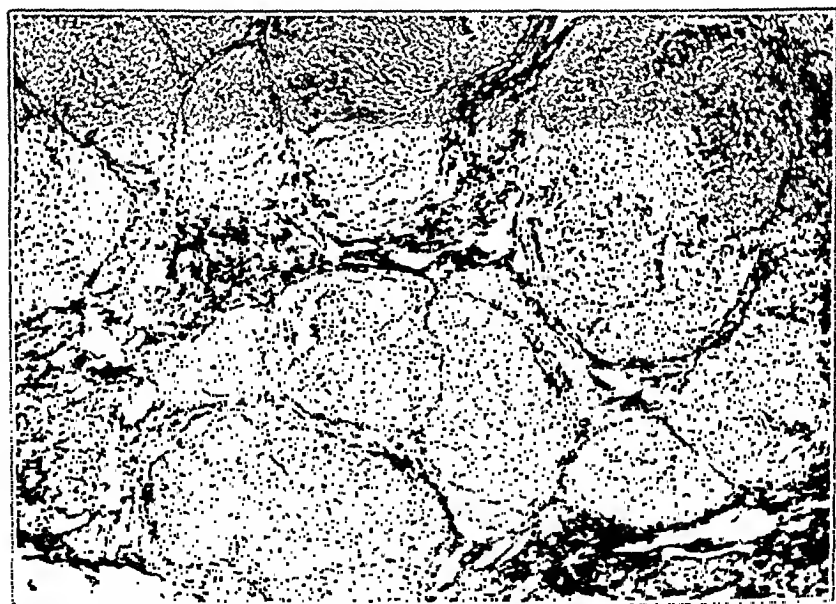


FIG. 5.—Cirrhotic liver of rabbit RM5. Note pseudolobulation, with fibrous tissue boundaries. Fibrous tissue replacing liver parenchyma (left lower corner). (X40.)

and/or green vegetables and carrots. It is certain, however, that this factor was not present in sufficient amounts in the orange juice given for its antiscorbutic effect. Neither is this unknown factor introduced in the 1% desiccated brewer's yeast supplement.

The typical liver cirrhosis produced in 1 guinea pig and 1 rabbit further suggests the relation of this diet to liver damage. It is known that cirrhosis of the liver is a chronic and slow-developing lesion and very frequently preceded by fatty degeneration.<sup>19</sup> We feel that our experiments may be throwing some light on the pathogenesis of portal cirrhosis in the human being. Patients that succumb to this lesion are not only consumers of large quantities of alcohol but are also neglectful of their diet. Patek<sup>14</sup> and others<sup>19</sup> have recently emphasized the therapeutic values of high vitamin feeding in clinical cases of "alcoholic" cirrhosis.

We are still in the dark as to the exact factor that is responsible for these changes but we are continuing the investigation. In addition to supplementing the diet with other foods that may contain the deficient factor, we are also decreasing the amount of fat in the basal diet. These animals may possibly be intolerant even to this moderate amount of fat. Gyorgy and Goldblatt<sup>9</sup> reported hepatic damage in rats on a diet that is deficient in one of the obscure fractions of the B complex, since the known factors did not prevent this damage. However, they admit that this lesion was not always predictable, and the pathologic changes were variable, only occasionally was fatty metamorphosis conspicuous. Their diet did not contain any cereal foods, such as is present in our diets. These foods (oats, wheat bran) are supposed to contain the complete B complex.

The effectiveness of choline as a lipotropic agent first became known because of its effect on the liver fat of depancreatized dogs.<sup>3</sup> Later, it was also shown that this substance is effective in preventing and curing the fatty livers produced by low protein and high fat diets in the rat.<sup>1,2,11</sup> Our animals satisfied neither of these conditions; they were not depancreatized nor was the diet poor in proteins. According to Best<sup>2</sup> 1 gm. of casein contains about 5 mg. of choline. With 30% skimmed milk powder in our diet, the amount of choline would appear to be sufficient. We administered an additional 20 mg. of pure choline to our animals daily, which in itself should be sufficient, since 5.6 mg. was found to be an adequate amount for 150 gm. rats on the low protein diet.<sup>2</sup> While the animals on choline showed some slight drop in liver fat as compared with the controls, the difference is not sufficient to make it likely that choline is the essential factor in this phenomenon.

Dragstedt and his co-workers<sup>6,7,15</sup> claim that their pancreatic extract contains a hormone, elaborated by the pancreas, which has a controlling effect on lipid metabolism and especially on the deposition of fat in the liver. Best and Ridehout<sup>2</sup> have shown

that the lipotropic effect of lipocaic on rats maintained on low protein diet can be explained on the basis of its choline content. Aylward and Holt<sup>1</sup> came to the same conclusion in rat experiments. Montgomery, Enteman and Chaikoff<sup>13</sup> and Ralli and co-workers<sup>16</sup> were able to produce fatty livers in dogs by ligating the external pancreatic ducts, thereby throwing doubt on the theory that an internal secretion is responsible for the deposition of fat in the depancreatized dog's liver. Without intending to enter into the controversy of the hormonal nature of lipocaic, we wanted to determine the influence of this pancreatic extract on our experimental animals. The administration of 475 mg. daily to a 500 gm. guinea pig was thought to be sufficient in view of Dragstedt's<sup>7</sup> earlier statement that 1.5 gm. of the extract was enough to prevent fatty liver in dogs probably weighing 20 times as much. The negative effect of the extract on our animals proves to us that this extract is not effective in preventing the fatty livers in our experimental animals.

**Summary and Conclusions.** 1. Fatty degeneration of the liver has been produced in the guinea pig and rabbit by apparently adequate diets, devoid of vitamin C.

2. Neither pure ascorbic acid nor orange juice has any prophylactic effect on this pathologic change.

3. An addition of 1% desiccated yeast and 10% dextrose was without effect.

4. Twenty milligrams of choline administered daily has slight effect in preventing deposition of fat in liver, while 475 mg. lipocaic was ineffectual.

5. Cirrhosis of the liver was produced in 1 rabbit and 1 guinea pig.

6. Some dietary factor is responsible for the development of the fatty degeneration and the cirrhosis. By implication, cirrhosis in man also may be due to a dietary deficiency.

7. Investigation is being continued to clear up some of the questions raised.

**Addendum.** After the completion of the above investigation, a recent publication by Rich and Hamilton<sup>17</sup> came to our attention. These workers report the production of fibrotic livers in rabbits on diets deficient in the B complex. On December 7, 1939 we put 4 guinea pigs on a diet which, in addition to the other ingredients, contained 10% desiccated brewer's yeast. One of these animals died April 20 and its liver contained 39% fat. The other animals are still (June 10, 1940) in good health and are taking the diet well.

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## ENDEMIC RIBOFLAVIN DEFICIENCY IN INFANTS AND CHILDREN.\*

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LITTLE could Blyth have realized in 1879,<sup>1</sup> when he described the yellow-green fluorescent pigment of whey, that brilliant research by a number of investigators in the years to come would show that it is an accessory food substance essential to the health and well-being of the higher forms of life. With the artificial synthesis of riboflavin in 1937, a milestone in the chemical research was passed, and this achievement opened a new vista for clinical investigation. Soon after it was synthesized it became available in sufficient quantities for clinical investigation, and during the past 18 months several reports on the effect of a deficiency of riboflavin in human beings have appeared in the medical literature.<sup>2,3,6a,5,10,12</sup> Although these reports are concerned with the disease in adults, it occurs in any age group, and from our studies we are convinced that among malnourished children diagnostic lesions of the disease are more common in the southern part of the United States than those of any other deficiency syndrome.

During the past 5 years we have been studying the natural course of development of deficiency diseases in an area in which they are endemic. In so doing, we have made clinical, laboratory and dietary studies of the entire family rather than of the individual patient,

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for within the family each member in general is subjected to the same dietary deficiencies. The information presented here will be restricted to that obtained from the study of infants and children who had diagnostic evidence of riboflavin deficiency.

During a period of 2 years, 472 children of parents with deficiency diseases were examined repeatedly, with particular attention directed toward their physical and mental development and toward the presence or absence of lesions characteristic of riboflavin deficiency. Without using special instruments or tests, we made a clinical diagnosis in each instance if one or more of the lesions characteristic of this deficiency were present. These lesions which in children appear similar to those seen in adults, include "cheilosis," the reddened macerated areas at the angles of the mouth and the linear lesions first described as responding to riboflavin by Sebrell and Butler,<sup>6a</sup> and the ocular symptoms characterized by bulbar conjunctivitis, lacrimation, burning of the eyes and failing vision, first found to respond to riboflavin by Spies, Vilter and Ashe.<sup>10</sup>

In children ranging in age from 5 months to 14 years we observed cheilosis in 113 cases, linear lesions in 93, and ocular manifestations in 167. These children were usually underweight, under-developed for their age. Many of them were apathetic and indifferent and had made poor progress in school. Frequently they complained of their mouths being sore and of their eyes burning and itching. The order of appearance of these symptoms was extremely variable and all did not occur in every case. Some children with advanced lesions of the eyes had no lesions of the corners of the mouth; others had severe mouth lesions whereas the eye lesions were slight. All these symptoms waxed and waned with the seasons and with changes in the quality of the dietary but they appeared most frequently during the spring and summer. Increased exercise and infections seemed to precipitate the appearance of lesions in the borderline cases. The response of children with riboflavin deficiency to synthetic riboflavin or to substances rich in it was gratifying. The cheilosis healed rapidly, the ocular symptoms disappeared, and the general health of the children improved. Unless therapy was continued or the diet improved, the disease tended to recur. The order of reappearance of the symptoms in any given patient invariably went through the same sequence with each recurrence, yet they varied greatly from patient to patient.

Laboratory studies showed that riboflavin is a normal excretory product when the diet is adequate, but when a severe deficiency exists the amount excreted is greatly diminished.<sup>9</sup> When the dietary intake is very low the excretion may for a time exceed the intake and, conversely, on a high intake the excretion may lag behind. In the absence of therapy, all the patients with advanced diagnostic lesions excreted less than normal persons of the same age, sex and size. Smears and cultures taken from the fissures at the

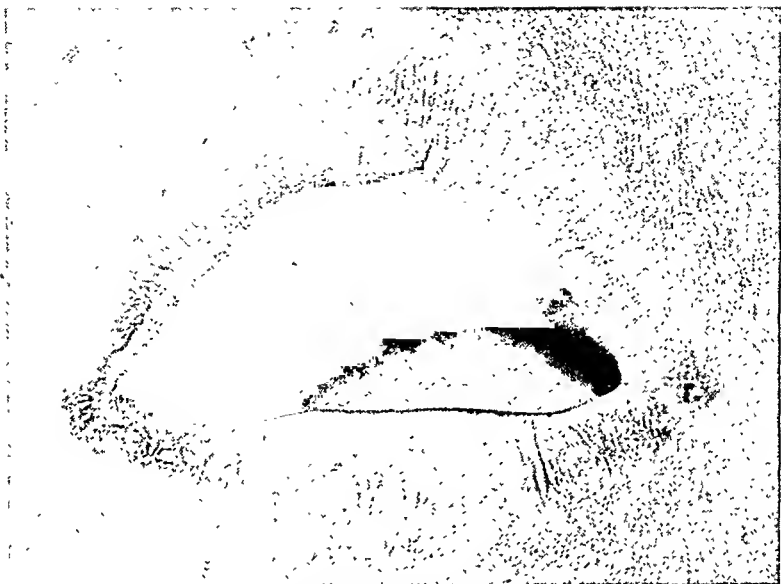


FIG. 1.—Note cheilosis at either angle of the mouth and the rather deep linear fissures of the lower lip.

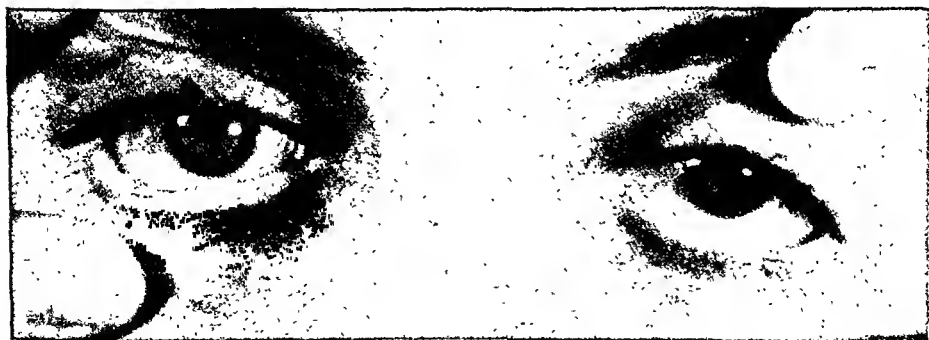


FIG. 2.—Note the violet hue of the eyes, which is most discernible in the right eye, and particularly the injection at the corners.



angles of the mouth showed either pure or nearly pure cultures of hemolytic *Staph. aureus* in 80% of the cases; *Strep. hemolyticus* was the predominant organism in the remaining 20% of the cases.<sup>5</sup> Hemolytic strains of *Staph. aureus* were isolated in 14 of 30 cases of conjunctivitis. *Corynebacterium xerosis* was found in a high percentage of the cases and was obtained in pure culture from the spots of Bitot in all of the 5 cases having these spots.<sup>4</sup>

The dietary studies showed that almost without exception the mothers of these children had subsisted on grossly inadequate diets during pregnancy and lactation. In some cases the mother's milk supply had been so meager that the infant was weaned soon after birth and given food which was inadequate for its nutritional needs, while in others the child nursed until it was 2 or 3 years of age. In every instance, they began eating food from the family food supply at the age of 2 or 3 months and were allowed to choose whatever foods they desired. The foods usually selected, because they are the ones most commonly used by the family, were biscuit, cornbread, gravy and syrup. Such foods habits had become firmly established at an early age and we found them difficult to change. Realizing that riboflavin is widely distributed in natural foodstuffs, at first thought we were surprised to find a deficiency of this substance so common. However, repeated dietary studies showed that the majority of infants and children in our study received only 35% of their estimated requirement.<sup>8</sup>

The following representative case history describes clinical riboflavin deficiency in a 14-year-old boy, and his response to treatment with brewers' yeast while he continued to eat his usual inadequate diet.

CASE 1.—C. A., the oldest of 8 children in a family in which the mother and father and each of the other children had lesions characteristic of riboflavin deficiency, was first seen June 8, 1940. He complained of soreness of the mouth, itching and burning of the eyes, and general weakness. This boy, like all other members of the family, subsisted on a diet consisting of bread, grits, dried beans, salt pork and syrup. The family occasionally had fruit, but never ate green vegetables. At times when milk and eggs were available, the children drank 1 or 2 glasses of milk and ate 1 or 2 eggs daily, but these foods were unavailable for months at a time.

Physical examination showed characteristic lesions of riboflavin deficiency, as evidenced by a large macerated area, 0.5 cm. across, at each corner of the mouth, at the outer edge of which a yellow crust had formed. A few superficial linear lesions were present on the lower lip (Fig. 1). The conjunctival vessels were greatly dilated and reddened, and the boy rubbed his eyes frequently. He had blepharospasm, and the injection of each eye was more pronounced in the lower half than in the upper half (Fig. 2). The inner surfaces of the lids were fiery red. No therapy was given the first week and it was observed that the lesions became worse. Riboflavin determinations on the blood, made by Miss Sue R. Stanbery, showed that his blood contained 0.32 gamma per cc. in contrast to the normal of 0.4 gamma per cc., as determined by the lacto-bacillus casei technique of Snell, Strong and Peterson.<sup>7</sup>

The patient was given 10 brewers' yeast tablets (Mead Johnson and Co.) t.i.d. (equivalent to 1 ounce of dried brewers' yeast). Within 5 days there was striking healing of the lesions around the mouth and in the eyes, despite the fact that throughout the study there had been no change in his dietary. The brewers' yeast supplement was discontinued and the dietary intake remained constant, and within 2 weeks there was a beginning recurrence of the lesions. The yeast tablets were again given in similar dosage, and the symptoms disappeared within 48 hours.

The following case shows clearly the development of riboflavin deficiency in a nursing infant and the response of both the mother and the infant following the administration of synthetic riboflavin to the mother without any change in the general dietary. It is of interest that the child also had a severe diarrhea of the type described by Spies, Walker and Woods.<sup>11</sup> The prompt relief of the child's diarrhea by giving the mother nicotinic acid indicates that the mother and certainly the child had nicotinic acid deficiency as well as riboflavin deficiency, though there were no lesions diagnostic of pellagra.

CASE 2.—Mrs. M. E., a 30-year-old white woman, came to the Nutrition Clinic of the Hillman Hospital July 2, 1940, complaining of weakness, headaches, nervousness and a sore mouth which had been present since the first of May. She brought her 23-month-old child, the youngest of 4 living children. The following history was given by the mother:

The child's maternal great-grandmother and 3 aunts had died of pellagra. For years the family dietary had consisted of large amounts of cornbread and biscuit and moderate amounts of dried vegetables, sugar, desserts and fat meat. During the summer they ate green vegetables 4 or 5 times a week. They drank buttermilk when they could get it, which was infrequently, and had not had any since the first of April. Each member of the family except the baby had an average of 2 eggs a week. They rarely had lean meat and never used butter. The mother complained of having been weak, nervous and irritable for several years, particularly in the spring and summer. For the last 14 years she had been pregnant or lactating or both, and she usually nursed her children until they were 24 months of age. Her first attack of clinical pellagra occurred in 1937 when she had been nursing her fifth child for approximately a year. In 1938 she had pellagrous dermatitis over her hands, forearms and arms.

Physical examination revealed a poorly developed, poorly nourished woman weighing 96 pounds. Her conjunctivæ were injected, as were the canals and bony landmarks of her ears. There was a whitish macerated area characteristic of riboflavin deficiency at each angle of her mouth. She was observed weekly over a period of 5 weeks, during which time the oral and ocular lesions became much worse. At the end of this time she was given orally 10 mg. of synthetic riboflavin (Mead Johnson and Co.) daily, and her diet remained unchanged. Within 2 weeks after therapy was initiated, the angles of her mouth had healed, the ocular lesions had improved, and she felt strong enough to do her own housework.

R. E., the 20-month-old daughter, had been on breast milk since birth, supplemented with biscuit, cereal, candy and sugar which she began eating at the age of 4 or 5 months. On a few occasions she was given orange juice. All spring she had been irritable and cross, and 2 months before she was seen in the Nutrition Clinic of the Hillman Hospital she began having intermittent diarrhea. (The diarrhea became much more severe during the next month.) When she was seen in the clinic, she had

cracks and fissures at the angles of her mouth, characteristic of riboflavin deficiency. Although the child was not treated, her lesions healed completely within 1 week after the mother's treatment was begun, a week earlier than those of the mother. The diarrhea continued but was relieved 1 week later following the administration of nicotinic acid to the mother.

**Summary and Conclusions.** 1. Repeated clinical, laboratory and dietary studies on 241 infants and children having characteristic riboflavin deficiency have convinced us that it is the most common clinical deficiency disease among infants and children in an area in Alabama in which deficiency diseases are endemic.

2. The mothers of these children usually subsisted on inadequate diets during pregnancy and lactation, and specific treatment of the mother with riboflavin or substances rich in riboflavin was curative for the lesions in the nursing infant.

3. Our studies indicate that riboflavin deficiency is a non-contagious, non-hereditary disease which occurs in either sex of any race. It develops over months and years, and the appearance of diagnostic lesions is preceded by a period of ill-health which should properly be termed the deficiency development time.

4. The response to specific therapy is gratifying in that every case was relieved by the judicious use of one of the specific therapeutic agents. Following therapy there is an increase in vigor and in sense of well-being and, in many instances, a striking increase in growth. The ocular manifestations disappear and the lesions around the mouth heal. As such lesions heal it becomes impossible to demonstrate the presence of *Staph. aureus hemolyticus* and *Strep. hemolyticus* which were prevalent before therapy.

5. The morbidity rate is greatly decreased when the physician makes the diagnosis early and initiates therapy. We find that the average case responds satisfactorily to the oral administration of 1 mg. of riboflavin t.i.d. or 1 ounce of brewers' yeast or liver extract daily. These substances have been given a sufficient period of time to warrant no hesitancy in recommending them as safe and effective therapeutic agents for the treatment of mother, infant and child. Despite the fact that the lesions of riboflavin deficiency were relieved while the general diet remained the same, we recommend the addition of liver, lean meat, and milk whenever possible.

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## BOOK REVIEWS AND NOTICES

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HEART FAILURE. . By ARTHUR M. FISHBERG, M.D., Associate in Medicine, Mount Sinai Hospital, New York City. Pp. 829; 25 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, \$8.50.

THE many merits that marked the first edition and made it an excellent and valuable book have been maintained in this enlarged edition. The book is practical, in a sense that will appeal to the practicing physician. The full and critical presentation of much physiologic and experimental data, upon which our modern conceptions of the nature of heart failure are based, also makes it a book of reference for the more specialized student of the circulation. T. M.

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PNEUMONIA. With Special Reference to Pneumococcus Lobar Pneumonia. By RODERICK HEFFRON, M.D., Medical Associate, The Commonwealth Fund; Formerly Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health. Pp. 1086; 18 figures, 181 tables and several maps. New York: The Commonwealth Fund, 1939. Price, \$4.50.

THIS imposing volume presents a comprehensive discussion of pneumonia, especially of pneumococcus lobar pneumonia, and the treatment of that condition. It is in part the outcome of the work of the Massachusetts Pneumonia Study. In the preparation of the book a very extensive literature was consulted and abstracted: there are cited nearly 1500 references. One finds here a thorough review of investigations dealing with the etiologic agent, its method of transmission, therapeutic measures, and the factors influencing recovery. This phase of the work will be gratefully received by the many workers in this active and vital subject. Yet so rapid is current progress in this field, that a supplement is already in order, for there are only 26 references to articles appearing in 1938, and none since that time. Nevertheless, the completeness of the material in all other respects and its well-balanced presentation stamp this as the outstanding and authoritative work on pneumonia. R. K.

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THE HEAD AND NECK IN ROENTGEN DIAGNOSIS. By HENRY K. PANCOAST, M.D., Late Professor of Radiology and Director of the Department of Radiology, University of Pennsylvania, EUGENE P. PENDERGRASS, M.D., Professor of Radiology, and Director of the Department of Radiology, University of Pennsylvania, and J. PARSONS SCHAEFFER, M.D., Ph.D., Professor of Anatomy and Director of the Daniel Baugh Institute of Anatomy, Jefferson Medical College. Pp. 976; 1251 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, \$12.50.

THIS publication is a volume of 976 pages which covers the Roentgen diagnosis of diseases affecting the head and neck very thoroughly. Included are 1200 illustrations of which more than 700 are negative prints of roentgenograms and photographs of patients and of basic technical procedures. Over 300 are illustrations which depict very clearly the anatomy of the head and neck and which show new aspects of these anatomic structures.

In the first chapter, the anatomy of the skull is described. The following chapters are devoted to fractures and dislocations; diseases of bone affecting the skull; tumors of the scalp, skull and cervical spine; the teeth and jaws; the nose and lacrimal passages; the paranasal sinuses; the temporal bone and affections of the mastoid and petrosa; intraorbital foreign bodies; intracranial tumors and cerebral pneumography. The last two chapters cover conditions affecting the cervical spine and neck.

The collaboration of the roentgenologist and the anatomist makes the volume especially valuable as there is no necessity for consultation of textbooks of anatomy, and in many cases the rationale of roentgen interpretation and procedure is made much clearer than would be otherwise possible. The anatomic illustrations are well chosen with this end in view. The authors in their preface state that, possibly, errors in judgment in selection of material may be noted. No such criticism, however, seems to be justifiable. For instance, the exclusion of variations in the skull occurring in the rare type of chondrodystrophy, known as gargoylism, cannot be regarded as of serious consequence. In fact, the omission of rarely occurring pathologic processes is of very infrequent occurrence, and as a comprehensive reference and textbook it cannot be recommended too highly. The effort of the authors to include only relevant facts and descriptions is reflected throughout the book. The bibliography at the end of each chapter is sufficient to afford the student ample opportunity to consult original source material. Of especial worth are the chapters on intracranial tumors, cerebral pneumography and the paranasal sinuses. The book is well printed and the illustrations are uniformly excellent and clear. The text shows careful editing with freedom from typographical errors.

After the illness and death of Dr. Pancoast, the burden of collection and composition of the roentgenologic portions of the book devolved upon Dr. Pendergrass. His long, painstaking labor is well rewarded by this publication of the finished product. The volume should be included in the library of every roentgenologist and it is most valuable, too, as a source of information on roentgen interpretation for the neurosurgeon, the otolaryngologist and other specialists.

R. B.

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AN INTRODUCTION TO BIOCHEMISTRY. By WILLIAM ROBERT FEARON, M.A., Sc.D., M.B., F.I.C., Fellow of Trinity College, Dublin; Member of the Royal Irish Academy. Pp. 475. Second Edition. St. Louis: The C. V. Mosby Company, 1940. Price, \$3.75.

THE AMERICAN EDITION of this book will be found valuable for students and teachers of biochemistry and as a reference book for practitioners of medicine. Although laboratory tests are included, nevertheless, the book is not intended primarily as a laboratory manual. The approach is different from the usual textbooks of biochemistry—the opening chapters being devoted to a description of the properties, occurrence and significance of the components of biologic materials. Included in this edition are special chapters on Steroids, Pigments (Pyrrole Derivatives, Carotinoids and Flavins) and Tissue Respiration.

F. S.

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THE RELATIVITY OF REALITY. By RENÉ LAFORGUE, M.D. Translated by ANNE JOUARD. Pp. 92. New York: Nervous and Mental Disease Monographs, 1940. Price, \$2.50.

THIS book deals with the following clinical psychoanalytic subjects: Concerning Anxiety, Conflicts in the Affective Development of Man, Relativity of Reality and Genesis of the Need of Causality, Reflections Concerning the Intellect, and Reflections on the Notions of Free Will, Liberty and Death. Anxiety is definitely in the foreground in phobias and hypo-



chondriasis, whereas it is in the background of obsessions, hysteria, paranoia, schizophrenia and frustration neuroses. Anxiety is an emotional state from which the individual attempts to escape. It may be normal and due to real danger, or neurotic, arising from the individual's peculiar psychic conflicts. Repression of the pathologic type is termed *scotomatization*. While Freud did not create psychoanalysis, he glorified it and his teachings for the most part are followed here. An exception is his statement that relation is an "illusion." The author says: "... religious beliefs appear from the psychoanalytic view point, as a necessary aspect of affective development, an aspect corresponding to reality which no scientific argument can devalue." Speaking of Einstein's relativity of time and space, the writer says: "We have ourselves added to this notion that of the relativity of reason, of truth or logic, of science . . . those concepts found to be of value to man, in ways economic as well as political and social."

This is an interesting contribution to psychoanalytic literature.

N. Y.

**THE PATIENT IS THE UNIT OF PRACTICE.** By DUANE WILLARD PROPST, A.B., B.S., M.D., Assistant Professor of Medicine, University of Illinois, College of Medicine. Pp. 219; 4 plates. Springfield, Ill.: Charles C Thomas, 1939. Price, \$3.50.

THIS book is a curious though at times interesting mélange of observations and reflections on the nature of disease, the defenses of the body, the elementary principles of psychobiology, an attempt to systematize physical diagnosis, a detailed account of history taking, and finally the author's diagnosis and treatment of many cases—mainly cases which presented organic symptoms but were best treated by psychiatric methods.

One wonders whether the author has attempted to arrange systematically a series of clinical lectures on a variety of topics, but for the sake of extended exposition in book form has added to the originals those features of his reading which have impressed him most. One notes that his hobbies include the constitutional background of susceptibility to disease and particularly the psychosomatic approach to diagnosis and treatment.

The book is entertaining but at times confusing. It may stimulate the student to look behind the presenting organic symptoms but not to investigate fundamental problems.

E. T. JR.

**PRACTICAL CLINICAL PSYCHIATRY.** By EDWARD A. STRECKER, A.M., Sc.D., M.D., Professor of Psychiatry and Chairman of the Department of Psychiatry, School of Medicine, University of Pennsylvania, etc., and FRANKLIN G. EBAUGH, A.B., M.D., Professor of Psychiatry, University of Colorado Medical School, etc. Section on Psychopathological Problems of Childhood. By LEO KANNER, M.D., Associate Professor of Psychiatry, Johns Hopkins University School of Medicine. Pp. 728; 55 figures. Fifth edition. Philadelphia: The Blakiston Company, 1940. Price, \$5.00.

THESE recognized authorities give considerable more attention to the psychobiologic hypothesis of Adolph Meyer in this edition, than in the preceding one. A well written chapter on the Psychopathological Problems of Childhood is included, and much additional matter on therapy and psychopathology is added. Whenever practicable, the case method is employed. On page 277, within four lines, marijuana is twice misspelled—mariahuana and marihuana; common usage may justify the spelling of the latter, but not the repeated use of the former. There now being many extra-mural psychiatrists, the Reviewer suggests the inclusion of some formal consideration of criminology, in the so-called complete text-books on psychiatry. This is a thoroughly revised edition of a deservedly popular text-book.

N. Y.

**THE DIAGNOSIS AND TREATMENT OF PULMONARY TUBERCULOSIS.** By JOHN B. HAWES, 2D, M.D., late President of the Boston Tuberculosis Association; Director of the National Tuberculosis Association, etc., and MOSES J. STONE, M.D., Assistant Professor of Medicine, Boston University, School of Medicine; Physician to the Chest Clinic of the Massachusetts Memorial Hospital, Boston, Mass. Pp. 260; 75 illustrations. Second edition, revised by DR. MOSES J. STONE, with a Foreword by the late RICHARD C. CABOT, M.D. Philadelphia: Lea & Febiger, 1940. Price, \$2.75.

THIS handbook has been written apparently for medical students and general practitioners who desire more information about the diagnosis and treatment of pulmonary tuberculosis than is available to them in single volume textbooks of medicine. The chapters devoted to the clinical aspects of tuberculosis offer less information than one might expect of even a small book written on this subject. Those concerned with treatment, particularly compression therapy, are sufficiently complete to serve as a useful source of reference. S. L.

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**A TEXTBOOK OF PHYSIOLOGY.** By WILLIAM H. HOWELL, PH.D., M.D., SC.D., LL.D., Emeritus Professor of Physiology in The Johns Hopkins University, Baltimore. Pp. 1117; 330 illustrations. Fourteenth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1940. Price, \$7.50.

IN this latest edition of his well known text on mammalian physiology, Professor Howell has maintained the high standard of excellent organization and simplicity characteristic of his earlier editions. By condensation of certain sections he has been able to bring new material into the text without significantly altering the total reading matter. The revisions and additions in the main are as follows: The chapter on the chemistry of muscular contraction has been revised, and that on electrical phenomena has been enlarged to include a brief discussion of Spike and After-Potentials. The chapter on the cerebrum has been somewhat rewritten, and that on the autonomic nervous system to include a more detailed discussion of the chemical transmission theory. The section on the ear includes a discussion paragraph on the cochlear response and the action potentials of the auditory nerves, and the section on the theories of hearing has been rewritten. In this section the subject of blood coagulation has been revised and a short paragraph on "shock" has been added. The main revisions include the interweaving into the story of digestion the possible function of vitamin K, reclassification of the amino acids to bring the number of known acids to 27, and some revision of the chapters on the kidney and endocrine glands. The main revision of this section involves the chapter on vitamins, in addition the discussion on carbohydrate metabolism and diabetes has been rewritten. M. M.

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**ENDOCRINE THERAPY IN GENERAL PRACTICE.** By E. L. SEVRINGHAUS, M.D., F.A.C.P., Professor of Medicine, University of Wisconsin. Pp. 239; 49 illustrations. Chicago: The Year Book Publishers, Inc., 1940. Price, \$2.75.

THE third edition of this monograph has been improved by revision. An excellent chapter on Endocrinopathies in Children and Adolescents has been added. It is the clearest and wisest presentation of endocrinology available for the student and practitioner. F. L.

## NEW BOOKS.

*Management of the Cardiac Patient.* By WILLIAM G. LEAMAN, JR., M.D., F.A.C.P., Assistant Professor of Medicine in Charge of the Department of Cardiology, Woman's Medical College of Pennsylvania, Philadelphia; Cardiologist, Woman's College, Memorial, Northeastern Hospitals and Philadelphia Hospital for Contagious Diseases, etc. Pp. 705; 255 illustrations. Philadelphia: J. B. Lippincott Company, 1940. Price, \$6.50.

*Laboratory Text in Pharmacology.* By ROBERT P. WALTON, Professor of Pharmacology, School of Medicine, University of Mississippi. Pp. 85. Philadelphia: J. B. Lippincott Company, 1940. Price, \$1.50.

This collection of experimental exercises, each accompanied by a brief discussion, is intended to serve in a supplementary manner to the more complete laboratory manuals and standard texts. . . . The exercises in many cases are of a demonstration character but they can be performed by student groups, particularly if the more involved demonstrations are given as special assignments well in advance of the scheduled periods. (From Preface.)

*De Morbis Artificum Bernardini Ramazzini Diatriba.* Diseases of Workers. The Latin text of 1713. Revised, with translation and notes by WILMER CAVE WRIGHT, Emeritus Professor of Greek in Bryn Mawr College. Pp. 549. Chicago: The University of Chicago Press, 1940. Price, \$5.00.

*The Author Publisher Printer Complex.* By ROBERT S. GILL. Pp. 76. Baltimore: The Williams & Wilkins Company, 1940. Price, \$1.00.

*The Medical Clinics of North America, Vol. 24, No. 5 (Boston Number, September, 1940).* Pp. 294; 22 illustrations. Philadelphia: W. B. Saunders Company, 1940.

This Boston number is made up of two symposia—the one on cardiovascular diseases consisting of 6 articles; the longer one on “diagnostic hints,” of 11 articles dealing with different systems of the body. The term has been very loosely interpreted by some of the authors.

*Die Amputationen der Oberen Extremität.* By HANS ISELIN-HAEGER, o. Professor für Unfallmedizin der Universität, Basel; FMH für Chirurgie, Orthopädie und Röntgenologie. Pp. 72; 66 illustrations. Basel: Benno Schwabe & Co., 1940. Price, Sw. Fr. 4.

*The Chronicle of Crichton Royal (1833-1936).* Being the Story of a Famous Mental Hospital During Its First Century, and Illustrating the Evolution of the Hospital Care and Treatment of Mental Invalids in Scotland. By CHARLES CROMHALL EASTERBROOK, M.A., M.D., F.R.C.P.E., Physician Superintendent, 1908-1937. With Foreword: Some Early Crichton Memories, by the late SIR JAMES CRICHTON-BROWNE, M.D., LL.D., F.R.S. Pp. 663; 103 illustrations and map. Dumfries, Scotland: Courier Press, 1940. Price, 25/-.

*Edinburgh Post-Graduate Lectures in Medicine, Vol. 1, 1938-39.* Pp. 513; illustrated. Edinburgh: Oliver and Boyd for the Honyman Gillespie Trust, 1940. Price, 10/6.

“A generous grant towards the promotion of post-graduate teaching received during the past two years from the Trustees of the late Mrs. Honyman Gillespie has been directly responsible for the appearance of this volume. . . . Thirty-three lectures were delivered by authorities upon their respective subjects. Originally published in the *Edinburgh Medical Journal*, they have since been submitted to the lecturers for correction before republication in the present volume. . . .” (From the Foreword.)

## NEW EDITIONS.

*Feeding the Family.* By MARY SWARTZ ROSE, PH.D., Professor of Nutrition, Teachers College, Columbia University. Pp. 421; illustrated. Fourth Edition. New York: The Macmillan Company, 1940. Price, \$3.75.

*Food, Nutrition and Health.* By E. V. MCCOLLUM, PH.D., Sc.D., and J. ERNESTINE BECKER, M.A., Professor, and Associate, of Biochemistry, School of Hygiene and Public Health, Johns Hopkins University, Baltimore. Pp. 127. Fifth Edition, entirely rewritten. Baltimore: By the Authors, 1940. Price, \$1.50.

# PROGRESS OF MEDICAL SCIENCE THERAPEUTICS.

UNDER THE CHARGE OF

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## SHORT WAVE DIATHERMY.

TWELVE years have elapsed since Schereschewsky,<sup>33</sup> Schliephake,<sup>34</sup> and others first reported on biophysical and clinical observations with ultra-high frequency oscillations, also described as short waves. Since in therapeutics there are also employed longer and shorter waves of the ultraviolet, infra-red and Roentgen ray portions of the electromagnetic spectrum, one cannot correctly speak simply of short waves without further qualification. In their physical and physiological effects the "short" waves of 30 to 6 meters (10 to 50 million oscillations per second) are next of kin to the 300 meter waves of "conventional diathermy" (1 million oscillations per second), and consequently in the United States the terms short wave diathermy for the former and long wave diathermy for the latter has been generally accepted. Kowarschik<sup>17b</sup> and others abroad have recently acknowledged the logic of the American terminology. The distinction originally introduced between short and ultra short waves has been largely discontinued in recent years and replaced by a simple statement of the wave length employed.

**Physical and Physiologic Effects.** There still exists some controversy as to whether the primary physical effect of short wave diathermy is due to anything else than heat. A few observers have described "athermic" effects and some hold that these effects depend on the electro-specific innate qualities of the substances treated. Hasche<sup>12</sup> has recently shown that tissue cells consisting of cultures of embryonic chick fibroblasts and osteoblasts could be killed by short wave diathermy under experimental conditions in which destruction could not be attributed to heat. He holds that the destructive effect of short wave diathermy occurs through diffusion and osmosis without liberation of electrons in contrast to Roentgen and radium rays which act through electron bombardment. Dognon<sup>8</sup> likewise believes that certain phenomena

like stimulation or inhibition of cellular activity cannot be explained on the basis of the thermal factor only.

The great majority of observers, however, regard short wave diathermy as a specific form of heat therapy which differs from long wave diathermy chiefly in the mode and extent of passage through tissues. The most striking physical property of ultra high frequency oscillations is their ability to pass through electrically conductive as well as poor conductive tissues. The heating of non-conductive substances in short wave fields is based on the phenomenon of dielectric permeability, and the higher the dielectric constant of a given substance the higher will be the capacity or strength of the electric field. Patzold<sup>29</sup> states that because of both conductive and "capacitative" heating by short wave diathermy, parts of the body which are closed off with poor conductors (fat, bones, and so on) such as inner organs, the spinal cord and the brain, will share in absorbing the electrical energy and hence they can be warmed without overheating the good conductive tissues which lie around them. This occurs especially with the shorter wave lengths below 10 meters. However, the wave length *per se* is not a marked factor in tissue heating in the living subject, as shown by Coulter and Osborne,<sup>4</sup> because differences in machines, the energy delivered to the patient and the technique employed exert an equally important if not decisive rôle.

In the early stages of investigation much was written about the possibility of selective heating effects by short wave diathermy at certain depths and in certain organs. This was based on the original report of McLennan and Burton<sup>22</sup> that for a given wave length there is a maximum heating effect which has a definite relation to the specific conductivity and dielectric constant of tissues. However, it was correctly pointed out by Mortimer<sup>26</sup> that the blood flow and the rapid interchange of heat in the living body may render the differences in temperature negligible for all practical purposes. Schaefer<sup>32</sup> finds that the only instance of practical import in which distinct variation may exist between the various body tissues is that encountered in fatty tissue in which overheating may be avoided by using the shortest possible wave length.

Specific bactericidal action has been claimed in the early reports of Haase and Schliephake,<sup>11</sup> but subsequent investigations have failed to corroborate such effects. Ozzano and Re<sup>28</sup> found with several species of pathogenic bacteria that short wave irradiation sometimes stimulated and sometimes inhibited their development and concluded that short wave diathermy exerted no selective specific action on bacteria but acted abiotically by heating the bacteria's environment. Hasche, Leunig and Loch<sup>13</sup> reported similarly.

Schereschewsky's original communication reported on lethal action on transplantable sarcoma in mice and attributed this to a specific biologic effect. Subsequently, similar claims were made by Reiter.<sup>31</sup> H. and M. Langendorff<sup>19</sup> repeated Reiter's experiments on induced tumors and refuted the theory that certain wave lengths have a specific action on tumors; they also found that any effect on tumor tissues was solely due to a rise in temperature in them and concluded that better results might be expected in treatment of malignant tumors by combined short wave and Roentgen therapy. On the other hand, Baumeyer<sup>2</sup> showed that coincident short wave and Roentgen treatment could lead

to the enlargement of malignant tumors and that short wave therapy was therefore contraindicated for malignancies.

Summing up all evidence available at present, it would appear that tissue heating is the only proved biophysical effect of short wave applications. Hildebrandt<sup>14</sup> investigated pharmacologic effects with short waves, assuming that in addition to a thermal effect on the tissues, chemical changes are also produced. The histamine content of dogs' blood was examined after treating the thorax for one-half to one hour with 3.5 meter waves. Specimens of blood taken at various intervals showed an immediate increase of several hundred per cent in some, while in others the maximum was reached only after two hours. A gradual return to normal value ensued in all in the next few hours. Diathermic tests yielded virtually the same results. Hildebrandt attributes the influence of the histamine content of the blood to the pronounced thermal effect of the short wave current.

**Clinical Applicability.** The advantages of the new techniques with the airspaced and inductance coil technique have led to the general acceptance of short wave diathermy as a simple and safe method of penetrating tissue heating. Beginning with Schliephake's first communications long lists of pathologic conditions were published in which short wave diathermy had been employed and found to be more or less effective. These observations usually were not controlled and paid no attention to the fact that in many of the enumerated conditions it is possible to achieve similar results with other and often simpler forms of heating. The Council on Physical Therapy of the American Medical Association<sup>1</sup> has also issued a list of its own and regards all methods of diathermy as equally applicable. Generally speaking, inflammatory conditions of inner organs, bones, joints, and bursæ form the logical field of attack by penetrating heat methods—long wave and short wave diathermy.

In the light of seasoned observation long wave diathermy holds its own very definitely, although for a while the enthusiastic reports on the newer method seemed to have doomed the contact plate technique of long wave diathermy to oblivion and manufacturers in fact have discontinued the making of long wave apparatus. As to definite reports on comparative results obtained with the two methods, Delherm and Fischgold<sup>7</sup> believe that short wave diathermy in the main gives results similar to those with long wave diathermy; it is useful especially for regions in which it is difficult to apply diathermy. In gynecologic conditions Waters<sup>36</sup> reported on a series of 82 cases of chronic inflammation, Kovesligethy-Buben<sup>16</sup> on 500 patients with acute and subacute inflammation, and Otto<sup>27</sup> on 174 patients, 74 with acute and subacute pelvic inflammation and 100 chronic. These clinicians generally state as an advantage of short waves their applicability and efficiency in acute cases, whereas long wave diathermy is only indicated in chronic cases. The contention that short wave diathermy is preferable in acute cases and long wave diathermy in chronic cases can be explained by the fact that, with the original air-spaced technique, as a rule mild heating was applied which is well tolerated and beneficial in acute cases. Long wave diathermy with the contact-plate method results usually in more intense heating, better suited to chronic cases. It is

quite problematical whether early experimental findings indicating that heating by short wave diathermy is more intense in the depth have any practical clinical meaning, because in actual practice the heating effect depends on a number of factors, such as size and spacing of electrodes, strength of the current, and length of treatment.

Kovacs<sup>15a</sup> states that short wave diathermy as usually applied with large size electrodes or an inductance coil results in a spreading of its lines of force over all adjacent structures with considerable wasted energy. This must be considered in treating heat-sensitive patients and such locations as the head or the neck where unnecessary heating of non-affected parts is to be avoided. Long wave diathermy should be preferable in treating superficially located muscles and bursæ, many of the joints, and the cervical spine, because it allows better localized heating.

Schliephake<sup>35</sup> and many of his followers regard purulent infections of the skin, furuncles, carbuncles, paronychia, dental abscesses and lung abscesses as conditions in which short wave diathermy, especially of the shorter wave lengths, affords striking relief of pain and speedy resolution. This has been corroborated in the case of facial furuncles by such American observers as Egan,<sup>9</sup> Brugsch and Pratt<sup>3</sup> and Laszlo.<sup>20</sup> Experienced clinicians, on the other hand, have emphasized that in all suppurative processes mild heating is sedative and recall that in acute conditions there is a natural tendency toward fairly quick recovery. Radiant energy in the form of Roentgen rays has repeatedly been reported as of special value in promptly reducing inflammation and hastening healing in furuncles and carbuncles (Meyer<sup>23</sup> and others). Kovacs<sup>15b</sup> reported years ago that in localized skin infection exposure to luminous heat repeated several times a day gives very marked relief and satisfactory resolution. The late E. P. Cumberbatch<sup>6</sup> was able to achieve similar results with long wave diathermy carefully applied. Schliephake himself advises only mild doses of short wave diathermy. Hence, definite proof of the alleged specificity of short wave diathermy in these conditions will be brought about only by comparative observations on a large series of controlled cases. So far no one has presented such a study.

Short wave provocation as a diagnostic aid in focal infections was proposed by Gutzeit and Kuechlin<sup>10</sup> who found an increase of the sedimentation rate in a case of active dental infection after applying short wave diathermy to the site. Such findings were corroborated by Liebesny,<sup>21</sup> while Pfankuch and Karpi<sup>30</sup> state that the response is individual and does not permit any definite conclusions. Hence there appears to be need for controlled research here also.

**Problems of Technique.** In the practical application of short wave diathermy, new problems have arisen which so far have been only partly solved.

A definite drawback of the technique of short wave diathermy as employed up to the present time is the lack of dosage guidance except as supplied by the patient's sensation. This crude method of dosage estimation, in spite of the necessity of applying varying dosages in different pathologic conditions, has generally resulted in the hit or miss manner of application by neophytes. During the past two years reports

of the successful construction of "dosimeters" for short wave diathermy have been presented by Mittelmann,<sup>24</sup> Mittelmann and Kobak,<sup>25</sup> and Kowarschik.<sup>17a</sup> These dosimeters indicate the actual absorption of short wave energy. They have not yet stood the test of general clinical use; and, of course, they add to the expense of the apparatus.

Orificial treatment with short wave diathermy to the prostate, seminal vesicles and to the female pelvic organs has been troublesome because of the difficulty of proper electrode spacing and dosage measurement. In long wave diathermy with metal contact electrodes inserted in the rectum, vagina or cervix uteri, it is possible to estimate dosage fairly accurately even without a thermometer, by the reading of the milliammeter. The skin sensation under the dispersive electrode is also an aid for the experienced, if the same set-up is employed. In short wave diathermy, none of these considerations prevails and the only safe guide is a thermometer inserted into the shaft of the orificial electrode showing that the rise of temperature in its immediate vicinity is within the safe estimated tolerance. The selection of the best type of active electrode whether insulated or not and the spacing of the dispersive electrode is also a problem, as any one having attempted such treatment with the variety of apparatus available will know. In Europe, glass enclosed electrodes are used for vaginal treatments. In the United States, the advice generally given is to administer orificial treatments with metal electrodes and long wave apparatus or else to use the induction coil technique. It is doubtful, however, whether heating the soft tissues by a single coil *in toto* from the skin inward will accomplish the same result as the combination of an internal and an external electrode.

Metal direct contact plates with short wave diathermy as first reported on by Kovacs<sup>15c</sup> offer a solution to some of the difficulties of technique. Their use is made possible by the introduction of extra condensers into the patient circuit of the short wave apparatus, thus compensating for the loss of spacing. While it involves the return to direct contact plate technique with the necessity of careful adaptation of the metal plates, its practical advantages are: 1, it permits the use of a simple milliammeter in the patient circuit and a fairly accurate estimate of dosage; 2, the treatment cables no longer form part of the receiving circuit and can be handled without drawing energy from them and without the danger of their overheating; 3, finally, it obviates superfluous scattering of energy into surrounding tissues as well as into space and also cuts down radio interference considerably.

Radio interference by short wave apparatus has been the subject of a national conference<sup>5</sup> and has been amply discussed by Williams,<sup>37</sup> Krusen<sup>18</sup> and others. Short wave diathermy causes interference in important short wave radio communications on land, and sea and also in television. With high powered apparatus and excess radiation into space this interference may extend hundreds of miles away from the apparatus. Any of the several remedies suggested—such as shielding the apparatus, installing "crystal control," use of only a certain frequency or wave length or to operate the apparatus only at certain hours—would add greatly to the cost of equipment or necessitate scrapping much of the existing equipment or restrict its extent of



usefulness. This matter is now subject to serious consideration as regards Federal control, and the medical profession is on the defensive to protect its legitimate interest, which antedates the advent of radio.

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### RADIOLOGY

UNDER THE CHARGE OF  
ALBERT MILLER, M.D.

AND

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SECTION ON ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

### THE STOMACH.

THE stomach is an organ that is static and immutable but with an integrated and highly complex mechanism which must adjust itself continuously to the forces in its environment, both external and internal. Meteorologic forces such as changes in temperature, humidity, barometric pressure and the intensity of light are the most constant to which the individual must adjust himself. Dietetic factors such as lack of

intake or loss of certain vitamins or minerals play an important part as factors of gastric disorders. An individual who may be depleted of certain substances or changed chemically by other factors will react emotionally differently from another individual who is well buffered in his chemical and constitutional make-up. Emotional disturbances play an important part in producing both psychic and physical disturbances.

Drawing attention to these facts, Laing<sup>1</sup> discussed the clinical aspects of disorders of the stomach.

One of the disturbing features in the roentgenologic examination of the gastro-intestinal tract from the standpoint of the referring physician is the frequency with which the findings are negative. Over a period of years, in more than 70% of a group of cases in which the histories were carefully analyzed and the patients were sent for roentgenologic examination of the stomach at the Mayo Clinic because of suggestive symptoms, the findings were not positive. In somewhat more than 50% of the cases in which the findings were positive the lesions did not actually involve the stomach but were ulcers of the duodenum. Less than 15% of all patients examined, therefore, had lesions of the stomach itself to account for their symptoms.

Of the group of cases in which the roentgenologic findings were negative, operation was performed in approximately 5% in each year; in the great majority of cases the operation was performed for some other type of disorder and there was an opportunity to examine the stomach, at least by manual palpation, and no lesion involving the stomach was found. Of duodenal ulcers found at operation less than 2% in any year failed to produce roentgenologic findings. Of gastric ulcers found at operation less than 1.5% failed to produce roentgenologic findings. In the cases in which carcinoma of the stomach was found at operation, negative roentgenologic findings were obtained in less than 2% of the cases each year.

The ratio of the occurrence of duodenal ulcer, gastric ulcer and carcinoma of the stomach was 80 to 5 to 15 in that order. Organic lesions of the stomach, therefore, were found in approximately 20% of the cases in which the roentgenologic findings were positive. Of the organic lesions 15% were carcinomas; a small number of these involved the esophagus and some others involved the lower part of the esophagus and the cardiac end of the stomach.

Laing pointed out that the stomach of the intact human being is rather inaccessible and studies under normal and abnormal conditions are chiefly by indirect methods. In general, the methods of study were limited to: 1, the correlation of clinical symptoms with the pathologic findings so well brought out in about 1830 by Cruveilhier; 2, direct observation during surgical operations; 3, direct observation of the pylorus through gastric stomas such as made by Beaumont more than 100 years ago and recently by Carlson; 4, visualization of the stomach by means of Roentgen rays, following various procedures such as the giving of certain foods and drugs and noting their effects; 5, gastroscopic examination.

Laing felt that the symptom complex called "pylorospasm" merited much more consideration than it had received in the past. He defined pylorospasm as a spastic contraction of the thickened circular muscle

coat known as the pyloric sphincter, which at times produces various gastric disturbances.

In the roentgenoscopic examination of the stomach, pylorospasm may be a potential of considerable difficulty. It may simulate closely the roentgenoscopic image of carcinomatous involvement of the pyloric end of the stomach. To the experienced observer, it will suggest the presence of an ulcer, usually on the lesser curvature at some distance above the pylorus, and direct a careful search for further evidence in the way of a niche on the lesser curvature or the frequently accompanying incisura on the greater curvature side.

Laing stated that the etiologic factors in pylorospasm may be intrinsic or extrinsic. The most common intrinsic factor is a peptic ulcer of the stomach or duodenum. Under extrinsic causes he listed reflex factors due to organic lesions outside of the stomach. The reflex disturbance due to cholecystic disease is particularly interesting. Gall stones, which in themselves are producing no localizing symptoms, might be the basis for a so-called indigestion picture. It is commonly held that gall stones may remain for a period of years in the gall bladder without producing any symptoms. If a careful history is taken in all cases it will be found that patients with gall stones often have had attacks of so-called acid stomach or indigestion. Pylorospasm, in his experience, may be produced by a slight change in position of the stones. According to Laing, waiting for severe pains in such cases before instituting surgical investigation and removing the stones does not seem, in the face of clinical evidence, to be warranted.

Appendicitis is another important cause of pylorospasm. Reflex symptoms resulting from functional disturbances in other organs, such as the so-called irritable colon, are factors in causing pylorospasm. Laing quoted Smith and his co-workers as assured that the localized epigastric distress commonly associated with irritability of the colon is gastric in origin and is brought about by reflex stimulation of the stomach. Such findings agree with the observation of Carlson on animals, namely, that sufficient stimulation of all sensory visceral nerves may produce a contraction of the pylorus. Clinically, Laing wondered if the particular organ or structure having the lowest threshold is the one which produces the symptoms. Biliary dyskinesia (impairment of the power of voluntary movement) is another symptom complex which might be explained in the same manner.

Under systemic causes of pylorospasm, Laing listed the factors to which one must look for explanation of a considerable group of conditions in which the findings of the roentgenologic examination are negative in the face of a history of definite "indigestion." These factors are as follows:

1. Allergic states brought about by the ingestion of some of the more common offenders, as milk, eggs, and shell fish, to which the particular individual is sensitive. The gastro-intestinal manifestations have a marked similarity to those noted in bronchial asthma, namely, spasm of smooth muscle and edema of the mucous membrane.
2. Toxic states caused by the excessive use of tobacco.
3. Endocrine disturbances. Symptoms of dysfunction as manifested at the time of menstruation and the menopause are commonplace. The signs and symptoms associated with the neuromuscular imbalance in both hyperthyroid

and hypothyroid states often are encountered. 4. Diseases of the central nervous system such as locomotor ataxia may be an occasional cause. Gastric crises examined roentgenologically during an attack may show nothing but a pylorospasm. An organic lesion of the brain, such as a tumor, may be another productive agent. Psychoneurosis as a cause of pylorospasm occurs with much greater frequency than is at present suspected. If the spasm is of short duration in any of these conditions there may be no dilatation of the stomach, but if the spasm is persistent and prolonged, a dilatation may occur owing to the associated hyperperistalsis and hypersecretion.

An understanding of the mode of production of the patient's subjective symptoms and the way in which they may be modified by his environments, together with the taking of a careful history, is of great importance to the clinician and to the roentgenologist. There may be nothing abnormal noted on physical examination even in the presence of either a functional or an organic disturbance of the gastro-intestinal tract.

If organic changes are present, by roentgenologic examination the exact position and nature of the pathologic process are defined. If surgical measures are indicated they can be carried out at an early date, allowing a distinct advantage in prognosis. Whether surgical intervention is or is not indicated, subsequent examinations can be made in order to follow the results of therapy in selected cases.

Laing drew attention to the seasonal incidence of the symptoms in cases of peptic ulcer. Moynihan, he stated, emphasized this many years ago and stressed the constitutional type of individual in whom it occurred; Einhorn also was credited with stressing this fact and bringing out that in the majority of his cases the symptoms occurred in the spring and fall. During these seasons there is a greater variability of the meteorologic environment. This factor must play an important part in the reaction of the unstable individual who is afflicted with an ulcer. Laing quoted Preuner as finding that climatic conditions had a similar effect on asthma in his experimental work on guinea-pigs. Preuner found that the induced asthma was not dependent on such meteorologic factors as temperature, humidity or atmospheric pressure as long as these factors remained constant, but that during periods of rapid change in climatic conditions the average severity could be increased about 50 %. This new field of experimental meteorobiology may conceivably assume an important place in future gastro-intestinal and other studies.

Seasonal variations in the concentration of calcium, phosphorus and vitamin G in the blood occur. The iodine content of the thyroid gland in animals has been shown to vary markedly with the seasons. Clinically, other diseases and symptom complexes exhibiting periodicity are those of the skin, prostate gland, and certain types of asthma and hay fever, sinusitis, and shoemaker's tetany. Peterson and de Takats, Laing stated, have shown that pulmonary emboli are predominantly seasonal in their occurrence. Ulcers have been produced experimentally in the stomachs of dogs by the use of pitressin, in the exact situation in which they occur clinically in human beings. The blood supply to the tissue was diminished through increased tone or actual spasm of both muscle and blood-vessels, with subsequent digestion of the involved region and an ulcer thereby produced.

Laing's article was one of a series in a symposium on organic and functional disorders of the stomach. In the list of methods of examining the stomach he included gastroscopic examination. Although he stated that time did not permit full discussion of the subject, he furnished much food for thought to be applied to the study of the factors concerned in the production of functional gastric disorders. As heretofore stated, functional disorders must be responsible for the symptoms in the greater number of the approximately 70% of cases in which roentgenologic findings are negative. This group of patients is being more and more frequently subjected to gastroscopic examination. Where there has been opportunity to compare the results of roentgenologic examination and gastroscopic examination it was found that approximately 45% of the stomachs showing negative findings at roentgenologic examination showed some type of mucosal change at gastroscopic examination. This varied from changes which were interpreted as traumatic changes resulting from instrumentation in a few cases to frank alterations in the form of the gastric rugæ or definite changes from what has been recognized as the normal condition of the gastric mucosa. Organic lesions not elicited on roentgenologic examination were reported on gastroscopic examination in only 2.59% of the cases in this group; 2.3% gastric ulcers and 0.29% of carcinomas.

These facts would seem to indicate that there is a large group of cases of functional disorders of the stomach in which there is a definite field for the application of the knowledge compiled by Laing and that the means of recognizing these disorders are available in gastroscopic examination.

CHARLES G. SUTHERLAND, M.D.

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**Correction.**—The price of Dr. Roesler's "Atlas of Cardioroentgenology" is \$8.50 and not \$12.50, as stated in our October issue (p. 547).

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ORIGINAL ARTICLES.

ARTERIOSCLEROSIS OBLITERANS. A CLINICAL AND  
PATHOLOGIC STUDY.

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AND

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GANGRENE in the aged has been recognized since the earliest records of disease in man. It is a curious fact that for centuries gangrene did not undergo critical investigation. At best, references to this condition were brief and the conception of an obstruction in the artery by thrombosis was overlooked until the middle of the nineteenth century. Cruveilhier<sup>7b</sup> first described intra-arterial clots which occurred in cases of gangrene of the extremities. He erroneously ascribed the lesion in all cases to the presence of arteritis. The term "arteriosclerosis" seems to have been originated by Lobstein (1829-1833).<sup>7a</sup> The present conception of arteriosclerosis has been greatly influenced by the teachings of Virchow, and except for recent evidence concerning the importance of lipid metabolism in cases of arteriosclerosis, little progress since Virchow's time has been made in solving the causation of this disease.

The nomenclature of arteriosclerotic disease of the extremities is unsatisfactory. The terms "senile gangrene" and "diabetic gangrene" should be discarded. They represent a terminal process which in no way explains the underlying pathologic lesion. "End-arteritis obliterans" is a term that was coined in 1879 by von Winiwarter,<sup>10</sup> who described an entirely different lesion, a form of arteritis which now is recognized as thrombo-angiitis obliterans. "Atherosclerosis" is a term used for arteriosclerosis associated with extensive formation of atheroma. It is not a distinct entity. It is important to remember that the symptoms and manifestations of arteriosclerotic disease of the extremities are produced only by

insufficiency of arterial blood. This insufficiency is, in turn, the result only of obstruction of the arterial lumens and is not the result of degenerative changes in the arterial walls. Because of this, Buerger<sup>4</sup> suggested the term "arteriosclerosis with occlusion," and this term has been modified to "occlusive arteriosclerosis" by some students of the subject. "Arteriosclerosis with thrombosis" is not entirely correct, inasmuch as the occlusion is caused in part by atheroma as well as by thrombosis. "Thrombo-arteriosclerosis obliterans" is a good descriptive term but is euphonically too similar to "thrombo-angiitis obliterans." We believe that "arteriosclerosis obliterans" is the best term which has been used, because it is not too long and is sufficiently descriptive of the pathologic process to which it alludes.

**Material.** This paper is based on a clinical study of 280 consecutive cases of thrombo-arteriosclerosis obliterans which were observed at The Mayo Clinic in the years 1929 to 1933, inclusive. Undoubtedly, milder clinical forms have been overlooked in which one or more arteries of the extremities were involved without production of symptoms. Routine examination usually does not include determination of the presence or absence of pulsations in the peripheral arteries. Follow-up letters were sent to patients 3 years after the time of their first visit to the clinic.

The clinical data have been supplemented by detailed gross and histologic studies of the arteries obtained from 32 legs that were amputated because patients had arteriosclerosis obliterans. It is obvious that the lesions encountered in these legs represented for the most part end-stages in a pathologic process which had been present for many years. However, in a number of instances the advanced lesions were localized and it was possible to identify other lesions which we felt represented earlier stages of the condition.

**Etiology.** Arteriosclerosis obliterans occurs predominantly among men between the ages of 50 and 70 years. In the 280 cases, 240 of the patients were men and 40 were women, a ratio of 6 to 1. A similar sex ratio has been noted for coronary thrombosis, and by Allen<sup>2</sup> for a number of other diseases. This difference, however, is not so marked in cases of arteriosclerosis obliterans as it is in thrombo-angiitis obliterans, which has an incidence among women of less than 2%. The youngest patient in this series was 35 years of age and the oldest 96; 70% of the patients were between the ages of 50 and 70.

There is no significant difference in the racial incidence of the disease. Twenty (8.3%) of the 240 patients in whose history there was a statement of nationality, were Jews. This may be contrasted with a distribution of approximately 30% of Jews among the patients who have thrombo-angiitis obliterans and who come to the clinic. All the usual races found in the United States were represented in the group. The highest incidence of the condition was among the native-born Americans.

The most obvious causative explanation of the pathologic changes in arteriosclerosis of any part of the body is that of Virchow; the

presence of such changes represents wear or aging of arterial tissue as a result of stress and strain. Arteriosclerotic lesions are found with great frequency in the aorta and at the orifices of the branches of the aorta, structures that are subject to more than average degrees of intravascular strain, both constant and intermittent. Also, it is well established that arteriosclerosis develops prematurely among patients who have arterial hypertension. The fact that arteriosclerosis obliterans is so rare and so much less severe in the upper extremities than it is in the lower extremities may be explained by the fact that blood pressures are normally higher in the lower than in the upper extremities. It is obvious that there must be considerable hereditary differences in the ability of the arterial tissue to stand stress and strain, and this may apply not only to the arterial tree as a whole but to certain specific parts of the arterial tree.

Controversy exists as to whether the development of arteriosclerosis is entirely dependent on this hereditary weakness of the arterial tree plus stress and strain alone or whether other influences, chiefly certain metabolic and chemical disturbances of the body, might accelerate the development of the lesions if not actually cause them. Leary<sup>6</sup> and others have expressed the opinion that the atheromatous lesions of human beings may develop as a result of a disturbance in fat or cholesterol metabolism. The reasons for this are as follows:

1. Cholesterol and fat are constantly present in rather large amounts in the atheromatous plaques, even in the earliest stages of the development of such plaques. At the deep margin of the plaque there are often numerous lipophages in various stages of degeneration and destruction. Thus, the atheroma is very similar, histologically, to xanthomatous lesions, particularly those of the nodular type.

2. Atherosclerotic lesions, said to be indistinguishable from atherosclerotic lesions which affect human beings, can be produced in rabbits by feeding animal fat or cholesterol. In these instances severe lipemia and hypercholesterolemia develop as a result of the inability of the rabbits to metabolize animal fat successfully.

3. Arteriosclerosis obliterans is more common among persons who have diabetes and particularly among those who have ingested high fat diets than among persons who do not have diabetes, and it occurs prematurely among persons who have diabetes (this point is somewhat controversial).

4. In xanthoma tuberosum, a condition which is characterized by severe lipemia, and in a few isolated instances of lipemia unassociated with cutaneous xanthoma, the incidence of arteriosclerosis obliterans and coronary sclerosis has been high and the lesions have been rather extensive.

5. Studies on patients who had coronary and peripheral arterio-



sclerosis have shown that in many instances there is some increase in the quantity of the blood lipoids over that found in control subjects. This is more common among patients in the fifth and sixth decades of life than among older patients.

Data available at the present time would indicate that lipemia, even of mild degree, may accelerate the development of arteriosclerotic lesions but that it is doubtful that lipemia is a more important factor in the inception of such lesions than are stress and strain.

**Pathologic Findings.** The lesions of the arteries consisted essentially of three components (Figs. 1, 2 and 3): 1, atheromatous plaques in the subintimal tissue; 2, degenerative changes occurring in the medial coat; and 3, thrombosis. These three components of the lesion were present in unequal degree in different cases. Proliferation of elastic tissue between the intima and media was seen in very early lesions. More commonly the earliest lesion found was a small atheroma. In its earliest stages an atheroma appeared grossly as a slightly raised yellowish plaque on the endothelial surface of the artery. Histologically, there was a thickening between the internal elastic lamina and the endothelial layer which consisted of proliferated endothelial cells, fibroblasts, lipophages (foam cells) and considerable neutral fat (Fig. 4a). Advanced atheromatous lesions were often seen; they projected into the lumen for a considerable distance and partially but never completely occluded it. They were always relatively acellular and contained irregularly distributed deposits of fat globules, cholesterol, lipophages (Figs. 1, 2, 4b and 5), fibrous and hyaline tissue.

Thrombi were seen in all cases. They were always associated with formation of atheroma (Figs. 1, 2 and 5), although there was no relationship to the size or extent of the atheromas. The thrombi often completely occluded the lumen and they were often of various ages. Usually, layers of thrombotic lesions were seen in various stages of organization. In advanced lesions it was difficult at times to be certain of the character of the occluding mass, because organization and canalization of a thrombus simulated closely the appearance of atheroma.

In the medial coat the earliest degenerative changes which were noted were localized atrophy of the muscle fibers and replacement by collagenous fibers and proliferated collagenous connective tissue. Localized calcification was noted in many but not all of the arteries studied. In advanced lesions the entire muscular coat was found to be irregularly thinned and replaced in part by relatively acellular fibrous and hyaline tissue with or without deposition of calcium. In a few instances complete rings of calcium deposits were found similar to those seen in the so-called Mönckeberg's sclerosis.

No significant differences were noted in the lesions of arteriosclerosis obliterans among diabetic and non-diabetic patients. Thrombosis occasionally was seen in large veins (femoral, popliteal,

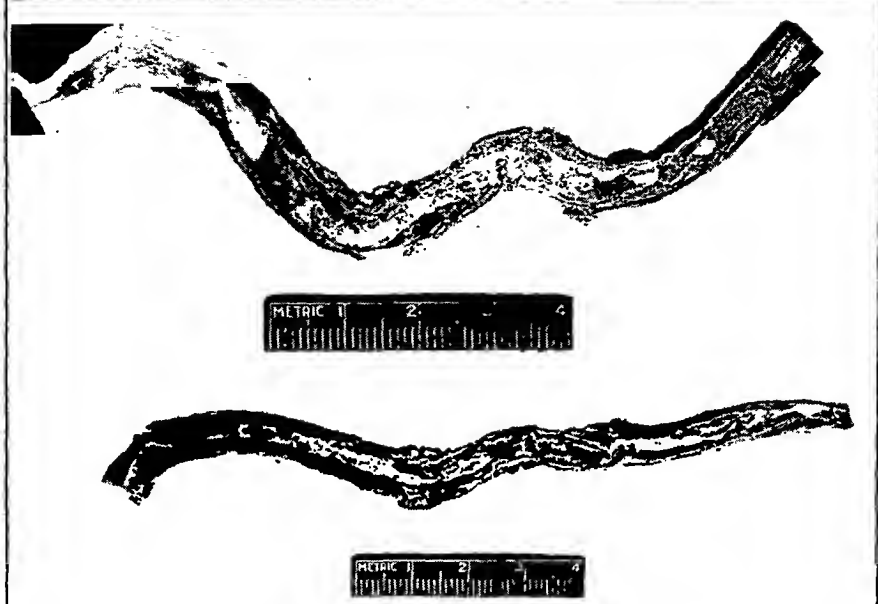


FIG. 1.—Popliteal arteries obtained from 2 patients who had arteriosclerosis obliterans (formalin and bisected longitudinally). Irregular atheromatous deposits (white) and thromboses of various ages (gray and black) are seen.

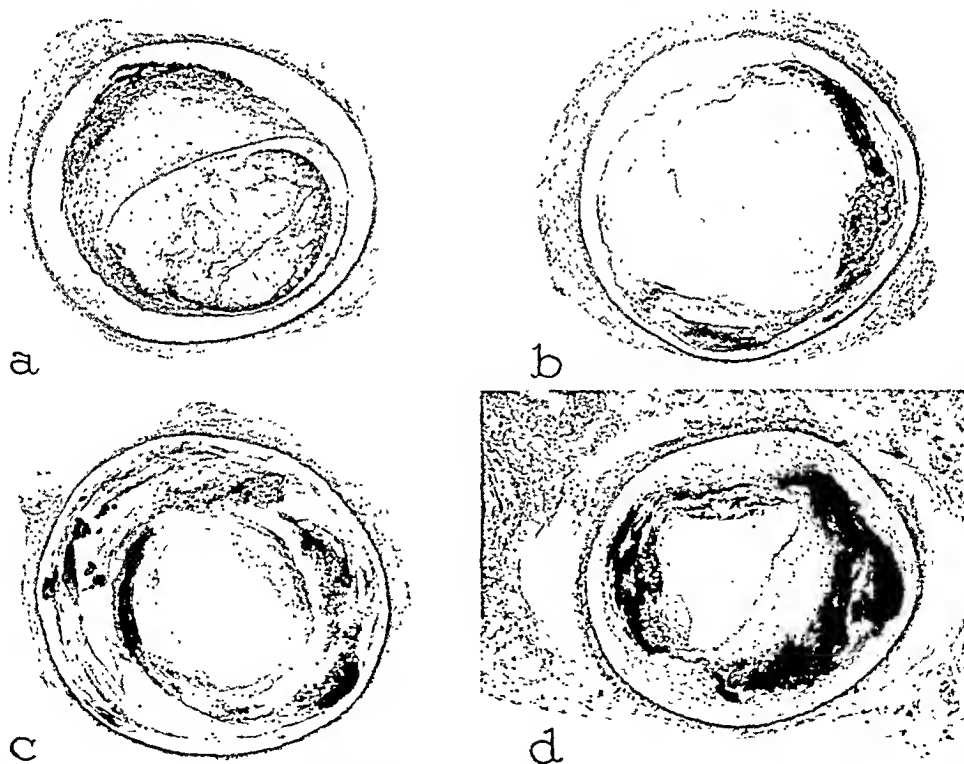


FIG. 2.—Cross-section of arteries (Sudan III and hematoxylin); a, popliteal artery ( $\times 10$ ) in which there is one small portion of calcification; otherwise, the medial coat is not much damaged; the lumen is partly occluded by an atheromatous plaque and partly occluded by an organized thrombus; the outer portion of the atheroma contains a large amount of fat; b, popliteal artery ( $\times 10$ ) in which the black deposits are fat; one may note irregularity of thickness of medial coat and splitting of internal elastic lamina; two stages of organized thromboses are shown; c, advanced atheroma and advanced degeneration of arterial wall of popliteal artery ( $\times 11$ ); d, posterior tibial artery ( $\times 16$ ) in which the black material is fat and indicates extensive formation of atheroma.

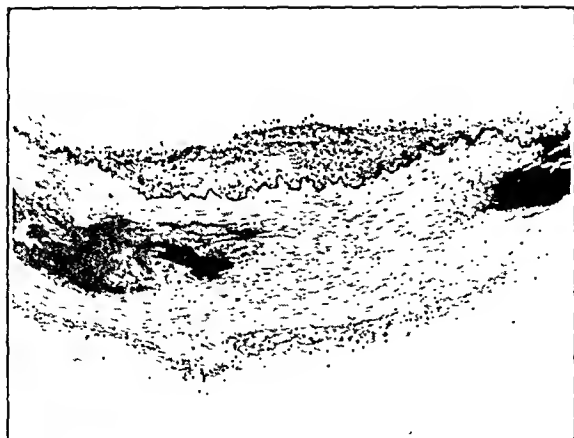


FIG. 3

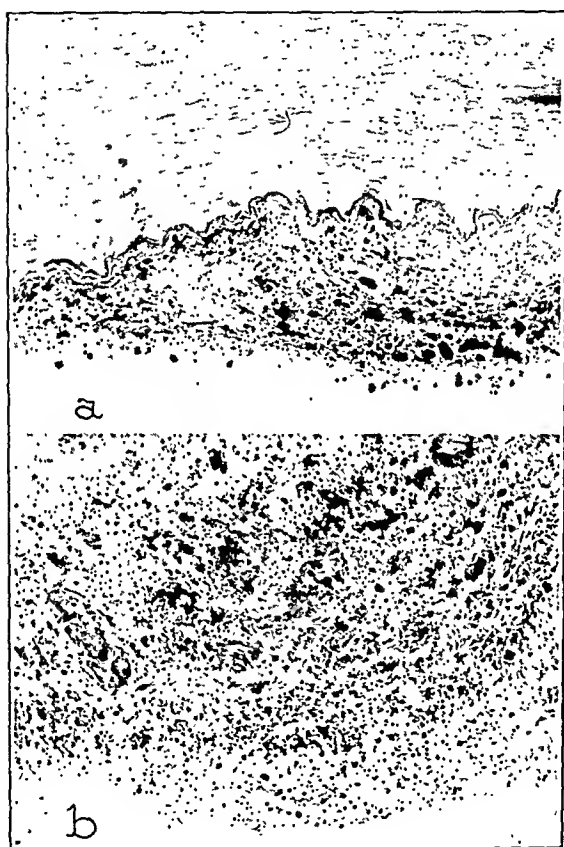


FIG. 4



FIG 5

posterior tibial) in cases of advanced arteriosclerosis obliterans or in association with acute and extensive arterial thrombosis.

The pathologic picture of arteriosclerosis obliterans is quite different from that of thrombo-angiitis obliterans and there should be no difficulty in distinguishing these two lesions. The important differential points are given in Table 1.

TABLE 1.—ARTERIOSCLEROSIS OBLITERANS AND THROMBO-ANGIITIS OBLITERANS: DIFFERENTIAL PATHOLOGIC FEATURES.

	Arteriosclerosis obliterans.	Thrombo-angiitis obliterans.
Medial coat	Marked degeneration with irregular thinning, fibrosis, hyalinization and sometimes calcinosis	Fibroblastic proliferation, but no degeneration and no calcinosis
Subintimal layer	Extensive atheroma formation with fat and cholesterol	No atheroma, no fat, no cholesterol
Thrombus	Often incomplete, with irregular and relatively acellular organization	Usually complete, with very cellular organization

Certain changes were noted in other tissues of the legs, and these changes were thought to be the results of ischemia. Often, atrophy of the skeletal muscles with replacement in part by fatty deposits or by fibrous tissue was present. In many cases there was considerable absorption of subcutaneous fat from the feet and toes. There were often thinning and atrophy of the skin and osteoporosis of the bones. Extensive Wallerian degeneration and fibrosis of the nerve trunks—*ischemic neuritis*—as described by Priestley,<sup>8</sup> were frequently seen. The gangrenous lesions were not materially different from any type of ischemic gangrene or gangrene resulting from ischemia plus trauma.

A recent interesting observation (Winternitz<sup>11</sup>) on the pathologic anatomy of generalized arteriosclerosis has shown that lesions of the arterial walls are often overvascularized rather than under-vascularized and that, apparently, foci of degeneration of the arterial wall may be initiated by hemorrhages into various portions of the arterial coats. These hemorrhages eventually may become calcified and give rise to the typical deposits of calcium which are seen in the medial coat. However, in arteriosclerosis obliterans, calcification and other forms of degeneration of the medial coat have no clinical significance in themselves, inasmuch as they do not cause significant interference with the flow of the blood (Fig. 3). Actual

#### LEGENDS FOR FIGS. 3, 4 AND 5.

FIG. 3.—Cross-section of posterior tibial artery. Extensive calcification of medial coat. Small atheroma. There was no thrombosis in this artery ( $\times 55$ ; H. and E.).

FIG. 4.—Cross-sections of posterior tibial artery (Sudan III and hematoxylin;  $\times 125$ ); a, early atheroma, showing deposits of fat (black) many of which are in lipophages; b, advanced atheroma, showing lipophages and fat globules.

FIG. 5.—Cross-section of atheroma of popliteal artery (H. and E.;  $\times 125$ ), showing foam cells (lipophages) at margin of atheroma and fresh thrombosis.

obstruction of the artery is begun by the atheroma and is completed by the thrombosis, and it is the degeneration and roughening of the inner surface of the atheroma which provide for the development of the thrombus. It is possible that other factors, such as alterations in the condition of the blood (polycythemia and thrombophilia), augment the development of these thrombi. It is doubtful, however, that in the swiftly moving arterial stream a thrombus ever forms without the presence of some lesion of the arterial intima as a starting point. Therefore, the most important component of the lesion present in arteriosclerosis obliterans seems to be the atheromatous plaque, because this plaque is responsible in itself for partial occlusion of the lumen and is the locus for the development of the thrombus which completes the occlusion.

**Symptoms.** Symptoms of arteriosclerosis obliterans of the legs are referable to diminished blood supply to the muscles, nerves and other tissues. The onset may be gradual or sudden. If the condition is chronic, intermittent claudication usually is the first symptom noted and it may persist for years without the appearance of other symptoms. The patient may be aware of an increased tendency of the foot to become cold, atrophic changes in the nails, or slowing of the growth of the nails. When the occlusive process is in the upper part of the femoral artery or in the iliac arteries and when it follows sudden occlusion of smaller arteries, ischemic neuritis may develop. The pain of ischemic neuritis has certain characteristics that aid in diagnosis. It is usually paroxysmal in nature and extends over or involves most of the leg or foot. The paroxysms are worse at night. Vasospastic changes in color occasionally accompany the bouts of pain and in some cases petechiæ appear in the skin over the painful region. The pain usually is influenced by position and usually is not influenced by the application of heat. Objective neurologic changes are rare and are found only in the most severe instances of the condition. In such cases, hyperesthesia, anesthesia, paralysis and loss of reflexes may occur. Paresthesia usually is not a primary complaint of patients who have arteriosclerosis obliterans. The occurrence of paresthesia in the absence of definite signs of arterial insufficiency is not sufficient reason for making a diagnosis of arteriosclerosis obliterans, because the paresthesia is more likely to be the result of vascular or senile changes in the central nervous system than of arteriosclerosis obliterans. As the occlusive process progresses, spontaneous gangrene or ulceration may develop; it usually occurs in the toes but may extend to the foot. More rarely, spontaneous gangrene or ulceration may begin on the skin of the lower part of the leg. In approximately 50% of cases the ulceration or gangrene is initiated by trauma, in the form of some crushing injury, laceration, wound, or in the form of thermal injury, such as a burn or frostbite, or in the form of chemical injury, often resulting from local medicinal applications.

*Distribution of Lesions.* The disease is usually bilateral, but at any stage its development is usually unequal; thus, the signs of circulatory insufficiency are more noticeable in one leg than in the other. Absence of pulsations in the posterior tibial, dorsalis pedis and popliteal arteries is the rule and in many instances pulsations are absent in the femoral artery in Scarpa's triangle. Pallor of the extremities on elevation and excessive rubor on dependency, particularly if these changes are unequal and if there is a definite delay in the return of color on dependency after elevation, are valuable signs of arterial insufficiency. There are often rather noticeable atrophy of the subcutaneous tissues and muscles of the calf and a shrunken appearance of the toes. These changes are more conspicuous as a rule in patients such as we are considering than they are in patients who have comparable degrees of arterial insufficiency caused by thrombo-angiitis obliterans. The first clinical evidence of arteriosclerosis obliterans may be the occurrence of sudden arterial occlusion caused by extensive thrombosis.

There is a marked difference in the presence of occlusion of the arteries of the upper extremity and of occlusion of the lower extremity. In only 3 instances in our series of cases was either the radial or ulnar artery occluded. About one-half of the patients who have thrombo-angiitis obliterans have occlusion of arteries of the arm. The rarity of occlusion of arteries of the arm in arteriosclerosis obliterans, as compared with thrombo-angiitis obliterans, is an important point in differentiating these two diseases. In 92 (67%) of the 137 cases in which the ocular fundi were examined, sclerosis of the retinal arteries or arterioles was present.

*Calcification and Occlusion of Arteries.* In a number of cases only one extremity had been affected by occlusion. This observation afforded an opportunity for us to study by roentgenography the amount of calcification present in the occluded and the non-occluded extremity. No direct relationship was found between the extent of calcification and thrombosis with occlusion. Calcification usually was as marked and as extensive in the non-occluded extremity as it was in the occluded extremity. However, a marked difference in the frequency of calcification existed between the sexes. The incidence of calcification among men was 69% and among women 31%.

*Diabetes Mellitus.* Diabetes mellitus was diagnosed in 57 (20.3%) of the 280 cases. This value may be somewhat low, because milder grades of diabetes may be overlooked if a glucose tolerance test is not performed. In 50 (31.8%) of the 157 cases in which the value for the blood sugar was determined the values were more than 120 mg. per 100 cc.

*Incidence of Trophic Ulcers and Gangrene.* Ulceration was present in 76 of the 280 cases and frank gangrene in 76, an incidence of 54% of the group studied. Among the patients who had diabetes,

the incidence of ulcers and gangrene (76%) was greater than among the patients who did not have diabetes. The majority of the diabetic patients had an extensive moist type of gangrene, secondary infection and frequently systemic reactions.

Ulceration and gangrene, when they occur, are usually of the dry type and are usually accompanied by little or no systemic reaction. Comparatively less pain is present than that which accompanies thrombo-angiitis obliterans. However, when diabetes is associated, the lesions exhibit a tendency to be moist and infected, considerable systemic reaction may be present and rapid development of ascending lymphangitis and septicemia may occur. In cases of the type under consideration, there seems to be a greater tendency for arteriosclerotic gangrenous and ulcerative lesions to spread and a lesser tendency for them to heal, than is the case with lesions of thrombo-angiitis obliterans, probably because of the fact that age has also impaired the vitality and resistance of the tissues.

*Ischemic Neuritis and Paresthesia.* Ischemic neuritis was noted in 22 (about 8%) of the cases. Numbness, tingling and hyperesthesia were the usual subjective complaints. Paresthesia was a significant complaint in 14 cases (5%). When it occurred, it was as likely to be present in an extremity with no occlusion as in an extremity with occlusion.

*Hypertension.* Hypertension, that is, a diastolic value of 90 mm. of mercury or more and a systolic pressure of more than 150 mm. of mercury, was found in 99 (35%) of the cases. This incidence undoubtedly is low, because many of the patients studied had a latent form of hypertensive disease or had had hypertension as demonstrated by the changes in the retinal arterioles. It is not uncommon to observe hypertensive changes in the retinal arterioles with normal or subnormal values for the blood pressure. The reactions of such patients to the cold pressor test indicate that hypertension exists in a latent form. Some patients undoubtedly have had elevations of blood pressure which have decreased to lower values following enforced rest and exhaustion and the use of drugs. In 18 cases of this group, the blood pressure was normal, but retinal findings indicated hypertensive changes. Including patients of this group, the incidence of hypertensive vascular disease in this series of cases was about 42%.

*Diagnosis.* The diagnosis of arteriosclerosis obliterans depends, first, on establishment of definite evidence of organic arterial insufficiency of one or both lower limbs. Almost all instances of chronic occlusive arterial disease of the lower limbs are caused by either thrombo-angiitis obliterans or arteriosclerosis obliterans, and in the great majority of instances if the first symptoms or signs appear after the patient is 50 years old, arteriosclerosis obliterans is responsible. However, in our series of cases the disease developed as early as the thirty-fifth year in 1 case. Other features which favor acceptance

of the diagnosis of arteriosclerosis obliterans over that of thrombo-angiitis are the absence of involvement of the upper extremities, the absence of superficial phlebitis, the presence of diabetes mellitus, the presence of hypertension, and the presence of roentgenologically demonstrable calcification of the arteries. A search for calcification should include the making of roentgenograms of the thigh and pelvis as well as of the lower leg. The presence of calcification is not *per se* evidence of arteriosclerosis obliterans or impaired circulation of the extremities. It is of importance only in differentiating between the different types of occlusive arterial disease. Roentgenologically demonstrable calcification is absent in approximately 30% of instances of arteriosclerosis obliterans. It may occur to a slight degree in the presence of thrombo-angiitis obliterans.

In case of doubt, the determination of the concentration of plasma lipoids may be of some help in the differential diagnosis of thrombo-angiitis and arteriosclerosis obliterans. Cholesterol values in the plasma in excess of 250 mg. and total lipoid values in excess of 650 mg. per 100 cc. favor the diagnosis of arteriosclerosis obliterans, particularly among patients in the borderline age groups. The values for plasma lipoids are not likely to be materially elevated in the aged, whether or not such persons have arteriosclerosis obliterans.

**Prognosis.** Persons who have arteriosclerosis obliterans have a shortened expectancy of life. Of the 116 patients concerning whom satisfactory follow-up information was obtained, 54.6% died within 3 years of their first visit to the clinic. The majority died in a manner which was suggestive of coronary thrombosis as the cause of death. Several causes are responsible because: 1, arteriosclerosis is a generalized disease and advanced degenerative foci may be present in arteries in other and more vital parts of the body; 2, the presence of diabetes and advanced grades of moist gangrene and cellulitis is accompanied by a fairly high medical and surgical risk; 3, persons who have advanced forms of arteriosclerosis are susceptible to intercurrent infections and the bronchial pneumonia of the aged.

It is interesting that in our series the mortality rate was not appreciably higher in the group of patients who had diabetes than it was in others. This was true in regard to both the group of patients who underwent amputation at the clinic and the group of patients whose condition was followed up after they left the clinic.

Of the 70 patients who required amputation, 24 had diabetes; of the latter group 1 died following operation, a mortality rate of 4.1%, as compared with 4.3% for the entire group. The most common cause of death following surgical amputation is some type of vascular accident. In another series of cases of diabetes studied by Allan and Kintner,<sup>1</sup> there was a surgical mortality rate of 9.3% following amputation in 86 cases. The study of these cases brought out the significant fact that patients who have arterio-



sclerosis obliterans and diabetes were subject to a mortality rate of 20% when amputation was done below the ankle and 7% when it was done through the lower part of the thigh or upper third portion of the leg. Secondary amputation was required in only 4 cases in the group studied by Allan and Kintner. In contrast to this, in 69 cases of gangrene and infection of the foot in which the patients were treated medically the mortality rate was 23%. The dictum "either operate early or operate high if diabetes is present" should be respected.

**Treatment.** The limited expectancy of life of patients who have arteriosclerosis obliterans should modify methods of treatment; it is one of the major reasons for not carrying out sympathetic gangli-onectomy for these patients. Such measures as fever therapy should be used with extreme caution, if at all, although the intra-muscular injection of sulphur may be used safely. Treatment should consist of prophylactic measures, methods to increase circulation, control of pain, and local measures to control ulceration and infection.

*Prophylactic Measures.* One of us (Barker<sup>3a</sup>) found that in 56% of a group of patients who had arteriosclerosis obliterans, ulceration or gangrene had been induced by accidental trauma or by injudicious therapeutic procedures. In 62% of the group of patients who had induced gangrene, amputation of a leg was necessary. Protection and proper care of the feet are of prime importance. Every effort should be made to avoid trauma to the toes or feet of the patient. New shoes should be "broken in" gradually. Felt shoes and heavy woolen stockings should be worn in cold weather. Chiropodic treatment should be administered with great care and with full allowance for the inadequate circulation present. Strong disinfectants and chemical compounds should never be applied to the feet. Local heat to preserve the warmth of the feet should be used with caution and preferably with the heating unit placed at some distance from the extremity. Trichophytosis should be treated with mild measures. Soaking the feet in a 1 to 8000 solution of potassium permanganate is safe and usually effective for the aforementioned condition. The use of tobacco should be discouraged because of its vasoconstrictor effect. When an elevation in the value for plasma lipoids is present, it is usually advisable to have the patient ingest a diet low in animal fats. This diet should consist of carbohydrate 420 gm., protein 60 gm., and fat 30 gm., of which 15 gm. may be animal fat. The diet should be supplemented by ingestion of 1 capsule of haliver oil a day. In a series of cases studied by one of us (Barker<sup>3b</sup>) there was a definite reduction in plasma lipoids in approximately one-half of the patients who had ingested this diet. It also may be possible to reduce the value for plasma lipoids by the careful administration of desiccated thyroid glands.

*Measures to Increase Circulation.* One of the main objectives in the treatment of occlusive vascular disease is to produce vasodilatation in that part of the vascular system still capable of expanding and thus to increase the blood supply to the affected extremity. Heat has long been known to produce vasodilatation. This may be applied locally in the form of radiant heat or to a distant part of the body as in the method of Gibbon and Landis.<sup>5</sup> In using any form of heat applied directly to the leg, great care should be taken to avoid having the temperature above 105° F. (40.5° C.) Postural exercises as designed by Buerger and Allen can be carried out easily by the patient and are of definite value in increasing the circulation. A mechanical oscillating bed has been devised which enables the patient to carry out the principle of the postural exercises without effort. The only advantage of this mechanical device is that it allows a more prolonged period of exercises than can be carried out by the patient. Short-wave diathermy applied to the trunk is of value in producing vasodilatation. However, it should be applied only by individuals trained in its application as the high frequency current may be dangerous if not properly used.

The production of fever by artificial means is one of the best methods of producing vasodilatation. The administration of typhoid vaccine is not advisable for most patients who have arteriosclerosis obliterans, because the reaction to foreign protein may not be well tolerated. An intramuscular injection of 1 or 2 cc. of olive oil containing 2% of sulphur in suspension is a safer method of producing fever than the administration of typhoid vaccine but has the disadvantage of causing considerable pain at the site of injection; however, this can be obviated partially by injecting from 1 to 5 cc. of a 1% solution of procaine with the sulphur-in-oil. Silbert<sup>9</sup> and others have treated many patients who had arteriosclerosis obliterans with intravenous injections of hypertonic solution of sodium chloride but have not felt that their results were as good as those obtained in similar treatment of patients who had thrombo-angiitis obliterans. In a warm environment, the use of mechanical methods of treatment such as intermittent suction and pressure or intermittent venous compression and the oscillating bed may improve the circulation. These methods were not in use during the time the group of patients under consideration was treated at the clinic; consequently, we were unable to evaluate the results of mechanical methods of treatment in this study. There is considerable difference of opinion as to the efficacy of this type of treatment. Certainly in most of our cases of arteriosclerosis obliterans in which efficient but safe methods of treatment are needed, mechanical methods have not been of as much help as was at first anticipated. Sympathectomy should be considered for the younger patients. The two-stage operation through a lumbar approach is preferable in cases of arteriosclerosis obliterans.

*Treatment of Pain.* Pain may be of two types, that is, intermittent claudication or rest pain. Patients who have no symptoms other than intermittent claudication have received extracts of pancreatic and muscle tissue intramuscularly with a subsequent increase in the distance they are able to walk, in many instances. A good plan for administering these extracts is to inject 3 cc. at each dose, once a day for 1 week, then twice a week for 4 weeks, and then once a week for 4 weeks.

Rest pain, particularly that of ischemic neuritis, may be very difficult to control. Alcoholic drinks equivalent to about 1 ounce of ethyl alcohol with 10 to 20 gr. (0.65 to 1.3 gm.) of acetylsalicylic acid is frequently as effective as any anodyne. Administration of opiates may have to be resorted to in some instances. Various mechanical methods of treatment, particularly the oscillating bed, may be of help in relieving rest pain. If simple measures do not relieve severe rest pain, section or crushing of the peripheral nerves of the leg may be performed. In some instances, this measure may afford enough relief of pain to delay amputation and allow prolonged trial of medical treatment. Intraspinal injection of alcohol may be tried as a last resort. If the pain is intractable, it may be wiser to amputate a limb rather than to subject a patient, whose expectancy of life is already limited, to a period of prolonged suffering and disability.

*Treatment of Ulceration and Gangrene.* For patients who have ulceration or gangrene limited to the toes, rest in bed is important. Warm foot baths at temperatures not exceeding 105° F. (40.5° C.) are useful in promoting drainage and allaying infection. Strong antiseptics should not be employed in the solution used for the foot soaks. A saturated solution of boric acid is usually satisfactory. A 0.5% solution of chloramine or a solution of potassium permanganate 1 to 8000 or weaker may be used. The period of soaking should be short and may be repeated several times a day. Warm packs, if applied cautiously, may be used when much infection or edema is present, but foot baths are preferable because of the danger of harming the ischemic tissues by other methods. When infection has abated and healing is beginning, a 1 to 1000 solution of thioglycerol may promote the formation of granulation tissue.

*General Measures.* It is important to maintain the patient's general health and resistance by rest, proper diet and treatment of anemia if it is present. Diabetes should be carefully controlled. If polycythemia vera is present, appropriate measures should be directed against it.

*Treatment of Sudden Occlusion.* When sudden occlusion of an artery occurs, emergency measures should be instituted. Any unnecessary delay endangers the chances of recovery of the patient.

The situation is somewhat like that of diabetic coma and the physician should remain in constant attendance until there is relief or an unfavorable outcome. Opiates should be administered at once to control pain. Aleoholic drinks usually are beneficial in relieving pain and may aid also by relieving arterial spasm. The head of the bed should be elevated and the leg placed in a dependent position in order to use the effects of gravity in increasing circulation. The limb should never be elevated. The extremity should be wrapped in cotton, which can be held in place by a roller bandage, to conserve its natural warmth. Heat may be applied by using a cradle with an incandescent bulb in it. Great care should be taken to avoid excessive heat. The temperature of the air about the extremity should be maintained at about  $32.2^{\circ}\text{C}$ . ( $90^{\circ}\text{F}$ .). Heat never should be applied directly to the skin. A vasodilator should be administered to relieve arterial spasm when it is present. Papaverine hydrochloride, a vasodilator, administered intravenously in doses of  $\frac{1}{2}$  gr. (0.032 gm.) may produce improvement in circulation. If improvement in circulation is noted (usually within a few minutes), the injection may be repeated in 4 to 6 hours. Care should be taken to see that the papaverine is active physiologically.

In cases of acute arterial occlusion there is grave danger of extension of thrombosis; consequently, intravenous infusion of heparin is a justifiable procedure as this is the only method which will certainly prevent thrombosis. If embolectomy is performed, heparin will prevent the thrombosis which may follow incision and suturing of an artery. The intermittent use of negative and positive pressure has been employed successfully in some cases as has the oscillating bed operated in a "hot room" in which temperature is maintained at  $32.2^{\circ}\text{C}$ . ( $90^{\circ}\text{F}$ .). Such mechanical methods should be used when available. In using the oscillating bed, it should be adjusted carefully so that there is a definite return of color to the foot during dependency.

*Amputation.* Conservative treatment may be of no avail in many cases, and amputation must be done, preferably before the patient's general condition has declined. Amputations of toes are likely to result in non-healing wounds, increase of pain and necessity for subsequent higher amputations, and are therefore rarely advisable in cases of arteriosclerosis obliterans. The prognosis for the healing of gangrenous lesions in this disease is so poor that it is probably wisest to amputate in the majority of cases if employment of conservative treatment for a few weeks has not resulted in definite improvement or in cases in which pain cannot be controlled and in cases in which gangrene has extended into the foot. Amputation of the extremity below the knee may not be successful, and if a second amputation is necessary, there is a considerable increase in operative risk. Furthermore, as has already been

pointed out, expectancy of life in this group of patients is limited. Hence, if amputation is done at all, it is usually advisable to amputate above the knee. Diabetes mellitus, when present, should be rigidly controlled. The problem of gangrene in arteriosclerosis obliterans in the presence of diabetes is definitely more complicated than in other cases because infection and septicemia may develop rapidly. When gangrene is present in patients who have associated diabetes, it is not advisable to delay, for a long time, performing amputation; when amputation is done, it should be done above the knee.

Seventy (25%) of our series of cases underwent amputation of a leg at the clinic because of the presence of frank gangrene with or without diabetes. Amputation usually was performed as quickly as conditions would permit. The aforementioned percentage does not produce the correct ultimate figure because amputation was necessary for at least an additional 5% of patients shortly after their dismissal. It seems likely that at least one-third of the patients who have thrombo-arteriosclerosis obliterans lose one limb. This does not include patients who should undergo amputation but for whom it is contraindicated by an excessive surgical risk. In these patients death ensues within a short time.

**Summary.** A clinical study has been made of 280 consecutive cases of arteriosclerosis obliterans which were observed at the clinic. The clinical data have been supplemented by detailed gross and histologic studies of the arteries obtained from 32 legs that were amputated because patients had arteriosclerosis obliterans. The disease was found to occur predominantly among men between the ages of 50 and 70 years. There was no significant difference in racial incidence. The possible rôle of certain metabolic and chemical disturbances as etiologic factors has been emphasized. The lesions found in the arteries which were examined for pathologic changes consisted essentially of three components: 1, atheromatous plaques in the subintimal tissue, 2, degenerative changes in the medial coat, and 3, thrombosis. No significant difference was noted in the lesions of arteriosclerosis obliterans among diabetic and non-diabetic patients. The diagnosis and treatment are discussed in detail.

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HEART SIZE AND EXPERIMENTAL ATHEROMATOSIS IN  
THE RABBIT.\*

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THE relationship between cardiac hypertrophy and coronary sclerosis is still controversial, and much of the evidence in clinical and autopsy data fails to distinguish the possible effect of the associated conditions which might produce hypertrophy from the effects of coronary sclerosis *per se*. This has led Aschoff<sup>3</sup> to regard hypertrophy in senescence as independent of arteriosclerosis, and has caused Bell and Clawson<sup>5</sup> to maintain that coronary disease itself does not cause hypertrophy of the heart. The latter authors in fact suggest that it is more reasonable to believe that the development of coronary sclerosis in the course of hypertension tends to prevent further cardiac hypertrophy. Nathanson<sup>18</sup> could find no relation between the degree of myocardial fibrosis and heart size in 113 autopsied cases of coronary sclerosis and attributed all the cases of large hearts in his series to preëxisting hypertension. Likewise, Lisa and Ring<sup>15</sup> could not find any correlation between coronary disease and cardiac hypertrophy. Sutton and Davis<sup>26</sup> did not obtain any cardiac hypertrophy in dogs, followed for periods up to 319 days after experimental ligation of the coronary artery producing myocardial infarction. Horine and Weiss<sup>12</sup> found no evidence of cardiac hypertrophy in 20 patients followed clinically from 1 to 10 years subsequent to myocardial infarction, and Miller and Weiss<sup>17</sup> failed to find cardiac enlargement in 19 cases of advanced coronary sclerosis.

On the other hand, Stewart<sup>25</sup> observed cardiac hypertrophy after producing injury of the heart muscle by repeated injections of epinephrine. Further, the enlargement of the heart observed in cases of arterio-venous aneurysm was attributed by Lewis and Drury<sup>14</sup> to a deficient nutrition of the myocardium; and they postulated that this mechanism might cause cardiac enlargement in

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coronary vascular narrowing. It is now well established that anemias lead to cardiac hypertrophy.<sup>9,16</sup> The hypertrophy occurring in anemia, epinephrine and arterio-venous aneurysm, however, may result from the increased work of the heart present in these conditions. Apropos of this discussion, cardiac enlargement is known to occur in cases in which the left coronary artery originates from the pulmonary artery.<sup>1,6,11</sup> As to coronary disease, Parkinson<sup>21</sup> concluded that in 8.6% of a total of 128 cases, cardiac infarction appeared to be the sole factor causing enlargement of the heart, and Palmer<sup>20</sup> noted that coronary sclerosis sometimes resulted in cardiac enlargement, which was progressive at times. Bartels and Smith<sup>4</sup> found gross hypertrophy in 88% of 42 autopsied cases following coronary occlusion. However, Davis and Blumgart<sup>7</sup> noted little or no hypertrophy with lesser degrees of coronary sclerosis; a slight to moderate degree of hypertrophy with more advanced sclerosis; and a considerable increase in size with the advent of congestive heart failure. In 11 patients with arteriosclerotic heart disease and no evidence of failure, Nemet and Gross<sup>19</sup> found 7 with heart weights less than 400 gm., 2 with weights above 400 gm., and 2 showed generalized microscopic hypertrophy of muscle fibers.

Recently Shohet *et al.*<sup>23</sup> in an analysis based on 122 necropsy cases without other possible causes for cardiac hypertrophy, found that coronary sclerosis produced hypertrophy of the heart, the heart weight being a function of the degree of coronary sclerosis. Smith<sup>24</sup> noted that right ventricular hypertrophy could be demonstrated in dogs at necropsy after ligation of the anterior descending branch of the left coronary artery, while left ventricular hypertrophy could be shown at necropsy when the smaller branches of the left coronary artery were ligated. Leary<sup>13</sup> made the incidental observation that following the production of atherosclerosis in rabbits some of the hearts appeared definitely enlarged.

In view of this contradictory evidence it was decided to put the possibility of a relationship between cardiac hypertrophy and coronary sclerosis to a direct experimental test. For this purpose rabbits were selected, since it has been established that the production of atherosclerosis in this animal is a relatively simple procedure, and as Anitschkow<sup>2</sup> and Leary<sup>13</sup> have pointed out, the atherosclerotic process in the rabbit is generalized and includes definite coronary artery involvement.

**Method.** The experiments were carried out on 30 rabbits all less than 6 months of age with body weights varying between 820 and 2100 gm. For the production of atherosclerosis a high cholesterol diet was utilized, prepared by dissolving 25 gm. of cholesterol\* in 500 gm. of cottonseed oil. One hundred ten cc. of this mixture was added to each 500 gm. of cracked wheat, oatmeal or barley with added powdered brewer's yeast or a vitamin

\* We are indebted to Dr. D. Klein of the Wilson Laboratories for supplying us with some of this material.

B concentrate\* preparation to prevent any B avitaminosis. The animals were allowed as much of this mixture as they desired. In addition to the cholesterol feedings the animals were given fresh green vegetables twice weekly.

All the rabbits were kept on this diet for periods varying up to 4 months, at the end of which time those that survived were sacrificed. As controls 10 untreated rabbits were used. They were in the same age group and their body weights ranged from 675 to 2160 gm. Of the original 30 rabbits 8 died from intercurrent circumstances within 2 weeks after being placed on the special diet, and since gross and microscopic examination failed to reveal evidence of atherosclerosis, they were added to the 10 untreated rabbits making a total of 18 rabbits for the so-called control untreated group, Group A. Of the remaining 22 rabbits, 6 failed to develop gross or microscopic evidence of atherosclerosis after long continued cholesterol feeding (1 to 2½ months), and these therefore constituted a second so-called control treated group, Group B, which could be used to check the effect of the regimen. The remaining 16 rabbits which died from 1 to 4 months after the diet was started or were sacrificed after 4 months, all manifested atherosclerosis at necropsy which was graded arbitrarily according to degree, number and confluence of the subendothelial patches in the aorta as 1 to 4+. These animals constituted the so-called experimental group, Group C.

In every animal after death the heart and aorta were opened and carefully examined; the former for enlargement, gross myocardial infarction, and valvular deformities; the latter for atherosclerosis. The heart was then separated from the aorta, washed, dried with absorbent paper, and weighed. Sections of the myocardium near its base and the aorta were cut, fixed in 10% formalin for 24 hours and then stained with orcein for elastic tissue and hematoxylin-eosin. Frozen sections were cut and stained with Sudan III for fat. These sections were then carefully examined microscopically. To rule out the possibility of co-existent systemic arterial hypertension or aortic valvular deformity, arterial blood pressure curves were obtained with the Hamilton<sup>10</sup> technique at fast camera speeds on 4 rabbits of Group C anesthetized with nembutal, 25 mg./kg. intravenously; and these curves were compared with similar records obtained under identical conditions on 7 normal rabbits of Series A.

**Results.** The heart weights of all the animals are assembled in Table 1. It will be seen from this table that the heart weight in the control Group A varied from 1.9 to 5.8 gm., and only 2 hearts weighed more than 5 gm.; average heart weight in this group, 3.8 gm. A similar range and average was found in control Group B; the heart weight ranging from 2.1 to 6.6 gm., and only one heart weighed more than 5 gm.; average heart weight, 3.9 gm. The heart weights of the remaining 16 rabbits constituting experimental Group C were greater: they ranged from 3.8 to 11.2 gm. and 12 hearts weighed more than 5 gm.; average heart weight, 6.3 gm. It is thus apparent that atherosclerosis resulted in cardiac hypertrophy. This is shown more clearly in the distribution curve (Fig. 11), in which the number of cases in each range of actual heart weight is plotted in each of the three series of animals.

When the degree of gross atherosclerosis was correlated with the degree of microscopic coronary artery involvement, a rough parallel-

\* Supplied through the kindness of Parke, Davis & Co.



ism was found in the majority of instances. Furthermore, a rough correlation could be obtained between the degree of microscopic coronary atheromatosis and heart weight; namely, the greater the coronary involvement the heavier the heart, although exceptions were noted. To rule out the possibility that the differences in heart weight might be due to differences in body weight, the distribution

TABLE 1.—HEART WEIGHTS OF ALL RABBITS.

*Control Untreated Group A.*

Rabbit No.	Heart weight (gm.).	Necropsy body weight (gm.).	Days on diet.
1 . . . . .	4.9	2160	0
2 . . . . .	4.4	2160	0
3 . . . . .	5.2	2160	0
4 . . . . .	5.8	2160	0
5 . . . . .	4.2	1640	0
6 . . . . .	4.2	1700	0
7 . . . . .	4.0	1600	0
8 . . . . .	4.1	1820	0
9 . . . . .	4.0	1820	0
10 . . . . .	4.5	1860	0
11 . . . . .	3.6	1400	11
12 . . . . .	2.2	1250	7
13 . . . . .	3.9	1125	1
14 . . . . .	2.8	990	7
15 . . . . .	3.6	1220	1
16 . . . . .	2.9	975	7
17 . . . . .	1.9	500	5
18 . . . . .	2.1	675	4

*Control Treated Group B.*

19 . . . . .	3.3	1125	26
20 . . . . .	3.5	1050	51
21 . . . . .	4.8	950	68
22 . . . . .	3.6	1200	25
23 . . . . .	2.1	860	52
24 . . . . .	6.6	1350	78

*Experimental Group C.*

25 . . . . .	5.2	1050	47
26 . . . . .	3.9	825	85
27 . . . . .	4.8	1200	120
28 . . . . .	6.7	1550	119
29 . . . . .	7.7	1475	119
30 . . . . .	5.8	1600	120
31 . . . . .	7.0	2100	120
32 . . . . .	5.9	1050	86
33 . . . . .	6.3	820	84
34 . . . . .	5.0	1320	67
35 . . . . .	4.0	1000	69
36 . . . . .	5.5	1240	90
37 . . . . .	9.5	1820	90
38 . . . . .	8.0	2000	90
39 . . . . .	11.2	1550	90
40 . . . . .	3.8	1200	42

of the animals according to the ratio of the heart weight to body weight was analyzed as a distribution curve in the three series (Fig. 12). This figure definitely shows that the rabbits in experimental Group C had heart weight-body weight ratios well outside

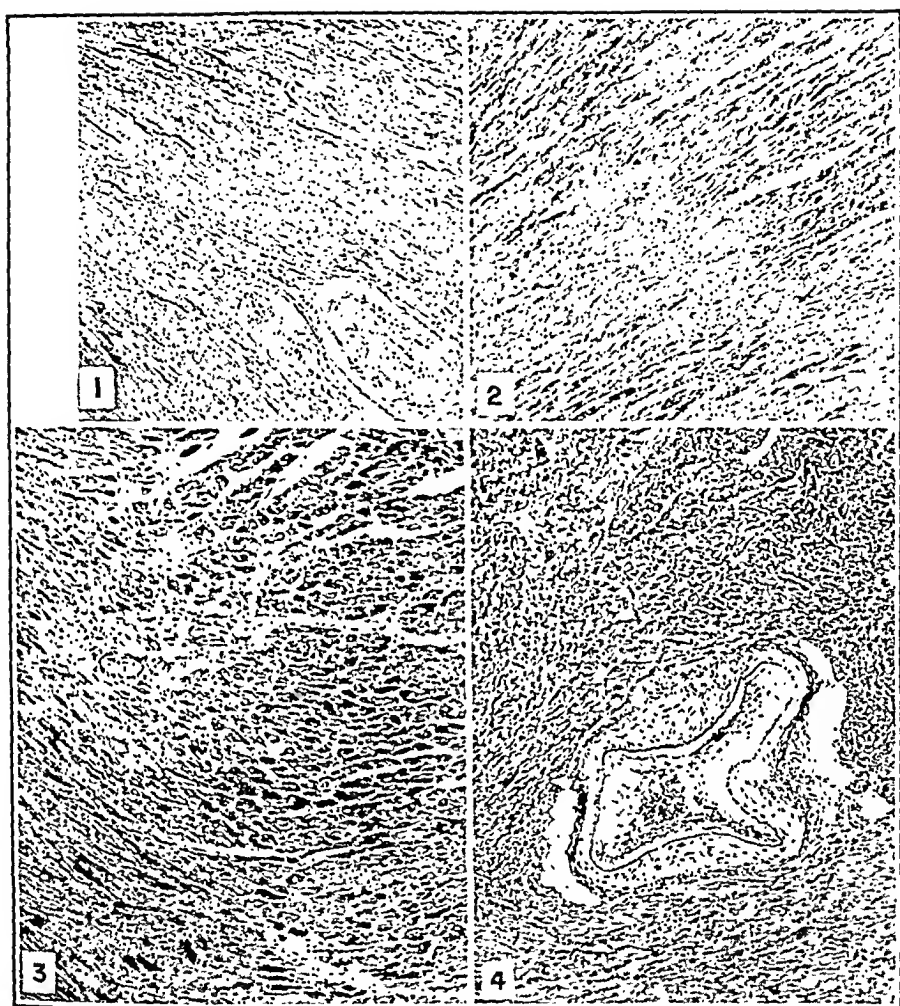


FIG. 1.—Myocardium of a rabbit of Group C (Weigert's iron, H. and E.—24 $\times$ ), showing a branch of the coronary artery with marked intimal proliferation.

FIG. 2.—Myocardium of a rabbit of Group C (Weigert's iron, H. and E.—24 $\times$ ), showing an extensive area of myocardial fibrosis.

FIG. 3.—Myocardium of a rabbit of Group C (Weigert's iron, H. and E.—40 $\times$ ), showing an extensive area of myocardial fibrosis and prominent vacuolization of the myocardial fibers.

FIG. 4.—Myocardium of a rabbit of Group C (Orcein, and iron-hematoxylin stain—36 $\times$ ), showing prominence of the internal elastic lamina and marked intimal and subintimal proliferation of the coronary artery

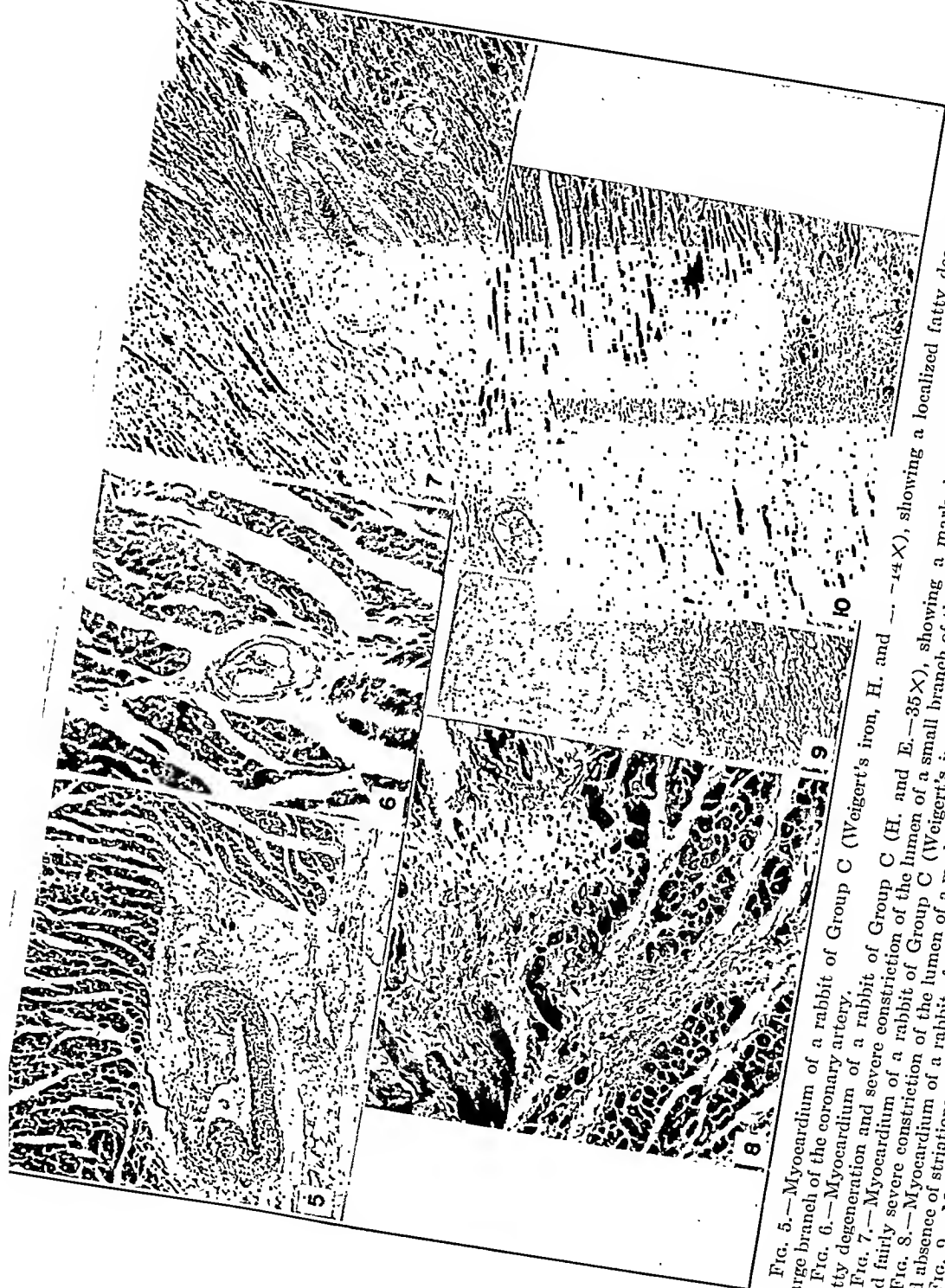


FIG. 5.—Myocardium of a rabbit of Group C (Weigert's iron, H. and E.—14X), showing a localized fatty degeneration of the large branch of the coronary artery.

FIG. 6.—Myocardium of a rabbit of Group C (Weigert's iron, H. and E.—35X), showing a marked fatty proliferation of the intima with absence of striations and nuclei of the muscle fibers in the upper portion of the photograph.

FIG. 7.—Myocardium of a rabbit of Group C (Weigert's iron, H. and E.—47X), showing an early myocardial infarction in the fibrotic region from relatively normal myocardium.

FIG. 8.—Myocardium of a rabbit of Group C (H. and E.—19X), showing an early organizing myocardial infarct with absence of muscle fibers and replacement by early connective tissue. The lumen of the small artery in this region is almost completely obliterated.

FIG. 9.—Myocardium of a rabbit of Group C (H. and E.—19X), showing an early organizing myocardial infarct with absence of muscle fibers and replacement by early connective tissue. The lumen of the small artery in this region is almost completely obliterated.

FIG. 10.—Myocardium of a rabbit of Group C (H. and E.—19X), showing an early organizing myocardial infarct with absence of muscle fibers and replacement by early connective tissue. The lumen of the small artery in this region is almost completely obliterated.

the limits of the animals in control Groups A and B, clearly indicating that the hypertrophy of the heart was not due to differences in body weight.

Microscopically, the lesions observed were similar to those described by other investigators,<sup>2,13</sup> and in the early stages consisted of the appearance of large pale cells filled with a lipid material in the form of fine and coarse droplets. This initial lipoidosis was observed in an intimal and subintimal location. In more advanced stages the lipid infiltration occasionally passed into the media and adventitia resulting in an apparent fragmentation of the internal elastic lamina. In some regions intimal and subintimal lipoidosis was so marked as to cause marked encroachment or almost complete obliteration of the arterial lumen (Figs. 1, 4, 6, 7, 10). Generally

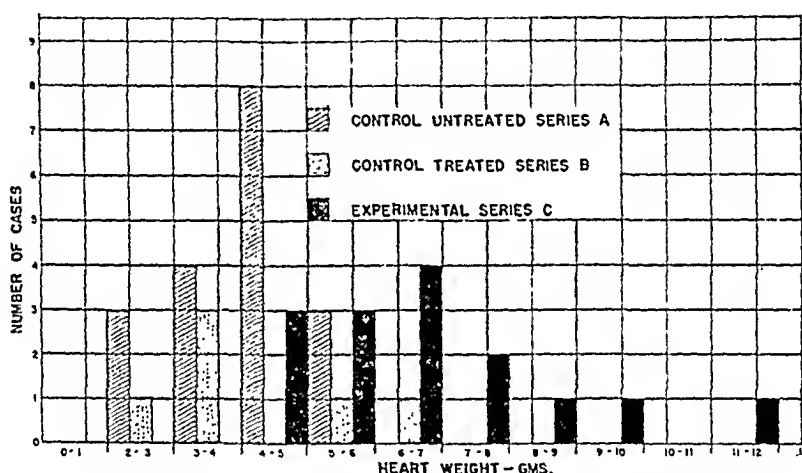


FIG. 11.—Distribution of the actual heart weights in the three series of rabbits. Note the heavier heart weights of those rabbits which developed atheromatosis (Series C).

it was the smaller coronary arteries which presented the most marked encroachment on their lumina, although the larger coronary vessels also presented the characteristic sub-endothelial lipoid infiltration histologically (Fig. 4). Not infrequently the subendothelial changes were patchy and plaque-like in nature presenting a picture rather characteristic of early human coronary sclerosis (Fig. 5). In addition striking changes were evident in the myocardium. These consisted of: 1, large areas where cross-striations could not be identified and pyknosis to complete absence of nuclei was noted (Fig. 8); 2, other areas where moderate to marked fatty degeneration was evident; 3, regions where increased amounts of interstitial connective tissue and patchy areas of myocardial fibrosis were present (Figs. 2 and 3); and 4, most striking of all, areas where very recent, acute organizing, and old myocardial infarcts were seen (Figs. 8, 9, and 10).

**Discussion.** Atherosclerosis of the aorta can be eliminated as a factor in the cardiac hypertrophy in our experiments, since it has been shown by Fahr, *et al.*<sup>8</sup> that the energy consumption of the heart and the external work of the left ventricle is not increased

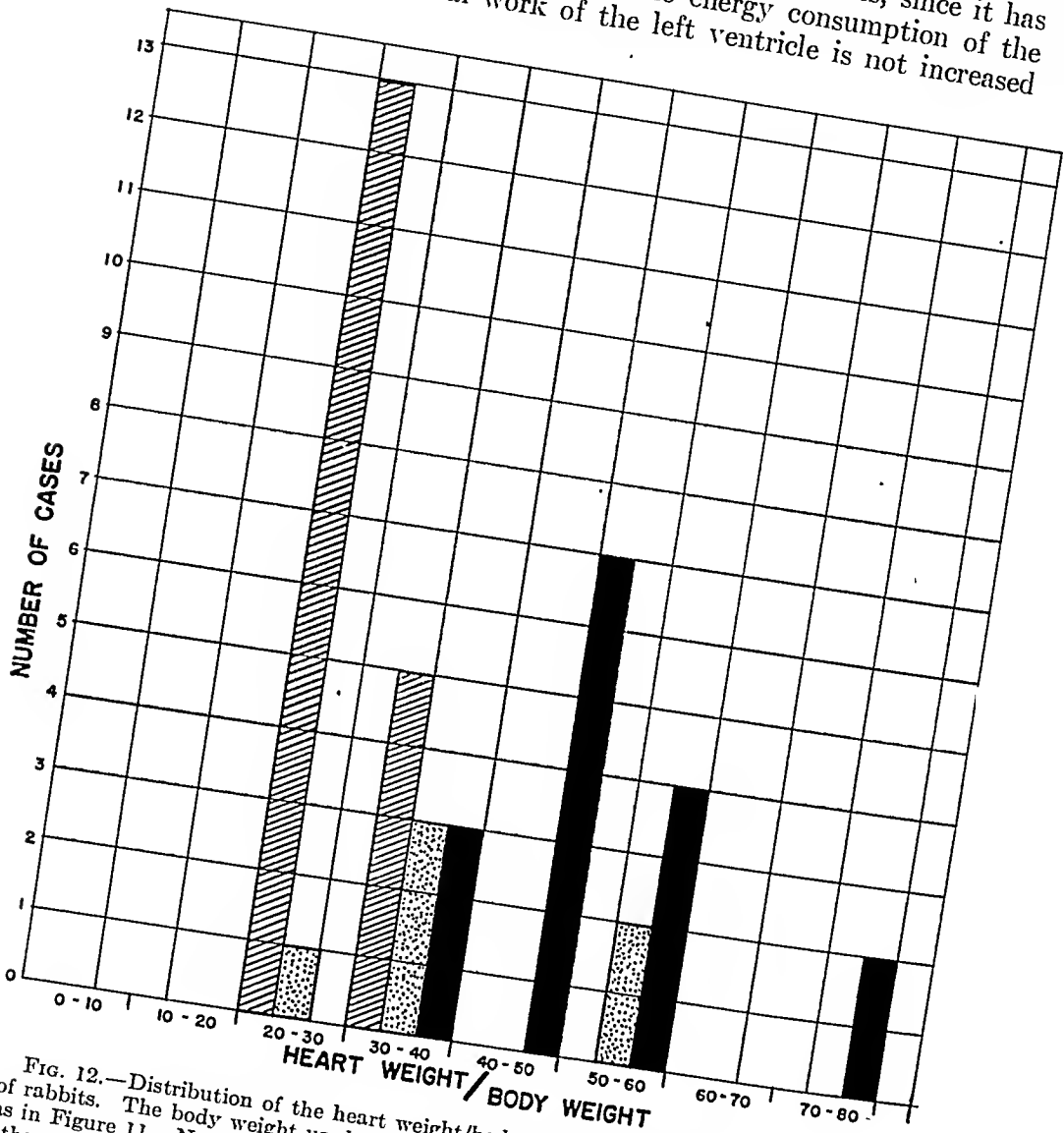


FIG. 12.—Distribution of the heart weight/body weight ratios in the three series of rabbits. The body weight used was that at the time of necropsy. Conventions as in Figure 11. Note the relatively heavier hearts of the rabbits which developed atheromatosis (Series C).

when the coefficient of volume elasticity of the large arteries is increased. Aortic valvular deformity, both stenosis and incompetence, can be eliminated, since normal pulse wave contours were obtained (*cf.* Fig. 13, *A* and *B*). Systemic arterial hypertension can also be excluded as an etiologic agent, since direct blood pressure

determinations showed the pressure to be in the normotensive range (cf. Fig. 13, *A* and *B*, and Table 2). Actually the blood pressure values fell in the range recently found to exist in the normal unanesthetized rabbit.<sup>22</sup>

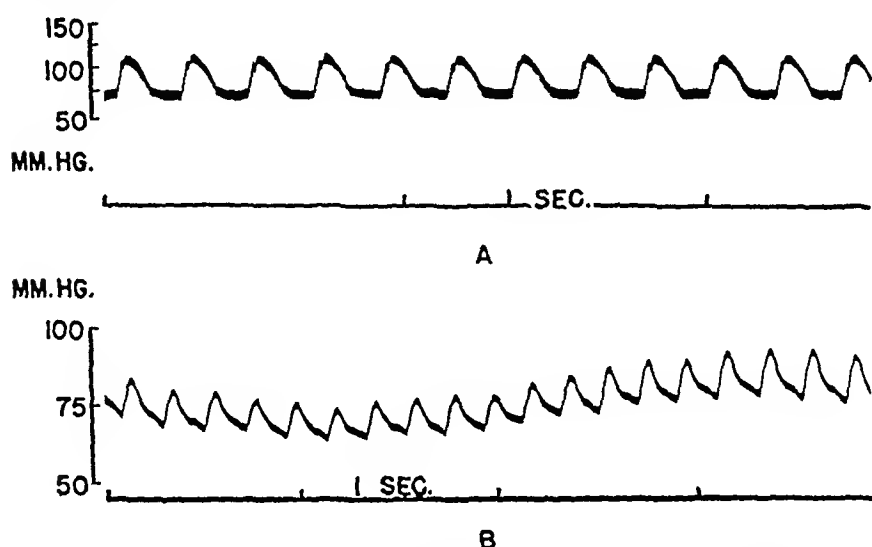


FIG. 13.—Femoral arterial blood pressure curves taken by a direct puncture (Hamilton technique) in a normal rabbit (*A*) and in one which developed atheromatosis (*B*) to show the similarity in contour and pressure levels. Ordinates show mm. of Hg; abscissæ, time in sec. Note the respiratory variation in blood pressure in *B*.

thetized rabbit.<sup>22</sup> There is therefore no reason to assume an absolute increase in the work of the heart as a result of hypertension, although the ischemia following coronary atheromatosis might be expected to lead to a relative increase in heart work even in the absence of

TABLE 2.—SYSTEMIC ARTERIAL BLOOD PRESSURE PRIOR TO SACRIFICE OF ANIMAL.

<i>Untreated Control Group A.</i>			
		Systolic pressure, mm. Hg.	Diastolic pressure, mm. Hg.
1 . . . . .		105	75
2 . . . . .		125	80
3 . . . . .		115	75
4 . . . . .		100	65
5 . . . . .		115	75
6 . . . . .		85	60
7 . . . . .		90	75
<i>Experimental Group C.</i>			
28 . . . . .		120	80
29 . . . . .		95	75
30 . . . . .		90-75	80-60
31 . . . . .		115	85

hypertension. It might be conceived that the increase in heart weight resulted from a fatty infiltration of the myocardium. Microscopic examination indicated, however, that when fatty changes occurred, they were in the nature of a secondary degenerative rather than a primary infiltrative phenomenon. Furthermore the possi-

bility of hypertrophy that might result from a vitamin B deficiency was avoided by mixing adequate amounts of brewer's yeast or a vitamin B concentrate with the diet, and histologically there was no evidence of a beri-beri type of heart. In addition, if a dietary factor *per se* were responsible, there should not have been the sharp distinction in heart weights between control treated Group B and experimental Group C. Finally, the possibility that the hypertrophy resulted from myocarditis, acute, subacute or chronic, was excluded by the absence of these conditions on microscopic examination.

It is thus apparent that the ischemia of the myocardium secondary to the induced coronary atheromatosis was the cause of the cardiac hypertrophy in our experiments. The exact *modus operandi*, whether it be through initial cardiac dilatation, through a relative increase in the work of the heart, through a direct effect of ischemia upon the myocardial fibers or their metabolism, or through a combination of all these factors, is not dealt with by our experiments.

**Summary and Conclusions.** 1. The relationship of cardiac hypertrophy to coronary sclerosis was made the subject of direct experimental study.

2. For this purpose 22 rabbits were fed on a high cholesterolin diet with the addition of the vitamin B complex. Sixteen of these rabbits subsequently developed moderate to severe atherosclerosis including involvement of the coronary arteries. The resulting heart weights of these were compared with 18 rabbits serving as untreated controls and with 6 rabbits, which although on the special diet, failed to develop gross or microscopic evidence of coronary or aortic atherosclerosis. All the rabbits were in the same age group with comparable body weights and the comparisons are therefore valid.

3. It was found that of the 16 rabbits developing atherosclerosis 12 showed heart weights of more than 5 gm. with an average cardiac weight of 6.3 gm.; whereas the 18 control untreated rabbits showed an average heart weight of 3.8 gm., with only 2 hearts weighing more than 5 gm.; while in the 6 remaining rabbits on the special diet but which did not develop atherosclerosis, only 1 heart weighed more than 5 gm., and the average heart weight was 3.9 gm.

4. To rule out factors other than the atheromatosis, direct systemic arterial blood pressures and pulse wave contours were obtained, and histologic sections carefully studied.

5. Evidence is presented to exclude atherosclerosis of the aorta, systemic arterial hypertension, aortic valvular defects, inflammatory disease of the myocardium and other actions of the diet as factors in the production of cardiac hypertrophy in our experiments.

6. It is therefore concluded that coronary atherosclerosis *per se* produces cardiac hypertrophy in the rabbit. Ischemia of the heart appears to be involved in some way in the mechanism.

We are indebted to Mr. J. Ransohoff for his technical assistance, and to Dr. O. Saphir, of the Department of Pathology, for his kindness in checking these microscopic interpretations.

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**METHIONINE AND CYSTINE, SPECIFIC PROTEIN FACTORS  
PREVENTING CHLOROFORM/LIVER INJURY IN  
PROTEIN-DEPLETED DOGS.**

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THE experiments listed below show clearly that methionine and to a less extent cystine prevent the liver necrosis of chloroform poisoning in the protein-depleted dog. Protein-depleted dogs may be fatally poisoned (with extreme liver necrosis) by 15 to 20 minutes of light surgical chloroform anesthesia. Given a few grams of methionine 24 to 4 hours before the chloroform anesthesia, the same depleted dog will show no evidence of frank intoxication or signs of liver injury following 40 minutes of chloroform anesthesia (Tables 3, 4 and 5). This is truly a remarkable protective reaction and deserves careful study and analysis. This reaction may give the answer to the puzzling question, How does chloroform cause hyaline liver necrosis?

In a recent report<sup>13</sup> from this laboratory it was demonstrated that liver injury due to chloroform anesthesia in the dog increases



in extent as the body protein stores are depleted. It was shown that a single large protein feeding protected a protein-depleted dog from injury by an otherwise fatal chloroform anesthesia. It was also shown that large amounts of the simple amino-acid glycine before anesthesia failed to confer any protection.

The importance of protein was recognized by Goldschmidt, Vars and Ravdin,<sup>7</sup> when as a result of their dietary studies on rats, they concluded that "A high protein diet previous to the anesthesia with chloroform reduces the incidence of hepatic cellular necrosis, even in livers with a high lipid content . . . ."

An interesting observation is recorded in the early experiments of Howland and Richards.<sup>8</sup> They described a marked increase in the neutral sulphur fraction of the urinary sulphur in dogs following chloroform anesthesia of 2 to 5 hours' duration. Since that time numerous investigators have demonstrated the biologic detoxication of a number of aromatic organic compounds by conjugation with cystine and elimination as mercapturic acids in the neutral sulphur fraction of the urine. Stekol's<sup>166</sup> demonstration of the detoxication of benzylchloride in the dog, rabbit, and rat to form S-benzylmercapturic acid indicates that detoxication by cysteine (or cystine) is not necessarily confined to strictly aromatic organic compounds.

**Methods.** All dogs used in these experiments were active healthy adults. As indicated in detail in the individual protocols, the dogs' reserve stores of protein were depleted by maintenance on a low protein diet consisting of cane sugar 71%, lard 15.1%, protein-free butter 7.2%, bone ash 1.8%, salt mixture<sup>6</sup> 1.8%, cod-liver oil 3%. Liver or lean beef 10 to 15 gm., yeast powder 1 gm., thiamine 150 I. U. and nicotinic acid 25 mg. were added as described in the individual protocols. The details of amounts and routes of administration of the amino-acid supplements are included in the individual protocols. When given intravenously the amino-acids were dissolved in saline containing 2 to 10 gm. glucose. At the beginning of the experiments the dogs' plasma protein levels were normal (6 to 6.5 gm. per 100 cc. with a few exceptions). The constant drain on body protein stores extending over a period of 4 to 14 weeks finally resulted in a lowered plasma protein level. A plasma protein level of 4 to 5 gm. per 100 cc. for at least 1 week before administration of the chloroform anesthesia was assumed to indicate a rather severe depletion of reserve protein stores.<sup>11</sup>

Blood samples were drawn from the external jugular vein with 1.4% sodium oxalate used as anticoagulant. Plasma protein determinations were carried out by the macro-Kjeldahl method on the oxalated plasma without correcting for non-protein nitrogen, fibrinogen was determined by micro-Kjeldahl, and icterus index by comparison of the oxalated plasma with standards prepared according to the method of Farahaugh and Medes.<sup>5</sup>

The dogs were given no food but water *ad libitum* 24 hours before the administration of the chloroform.

Anesthesia was induced with ether and then chloroform was given by the drop method. A light surgical anesthesia was maintained. All dogs recovered from the anesthesia quite rapidly and were conscious within 2 to 4 minutes.

**Experimental Observations.** In general terms we may say that a loss of appetite for a day or so may be due to ether anesthesia alone. When we observe that the icterus index rises and the fibrinogen content of the plasma falls after ehloroform anesthesia, we feel confident from the study of large numbers of animals with autopsy examination of the liver, that there will be found some liver injury. The degree of injury will parallel closely the fall in the fibrinogen levels. On the contrary, after ehloroform anesthesia when we find no icterus and no fall in the fibrinogen and a dog clinically undisturbed, we may safely assume absence of ehloroform liver neerosis.

TABLE 1.—PROTEIN, CYSTINE, AND METHIONINE PROTECT AGAINST CHLOROFORM POISONING.

Dog No.	Low-protein diet, weeks.	Preliminary treatment.	Duration of anesthesia, min.	Plasma protein level, mg. per 100 cc.	Fibrinogen.		Clinical condition.
					Before ehloroform, mg. per 100 cc.	48 hrs. after ehloroform, mg. per 100 cc.	
39-20	9	None	20	5.17	373	63*	Dead 40 hours
39-16	6	Lean beef	20	4.6-5.3	...	...	Normal
38-299	6	Lean beef	20	4.5-5.3	...	...	Normal
38-241	8	Plasma protein	20	5.2-6.3	...	352	Slight intox.
38-241	15	Plasma protein	20	4.7	370	205	Slight intox.
39-16	7	l-cystine	25	4.2	177	129	Slight intox.
38-169	6	l-cystine	27	5.0	235	260	Normal
38-340	12	l-cystine	30	5.0	223	160*	Moderate intox.
38-340	15	l-cystine	40	5.2	351	648	Dead 4 days
38-338	6	l-cystine	20	4.7	355	195	Slight intox.
38-338	13	l-cystine	40	4.6	237	166	Dead 4 days
39-157	9	dl-methionine	40	4.9	450	421	Normal
39-157	13	None	15	4.8	327	38*	Dead 36 hours
39-12	6	dl-methionine	40	4.5	264	222	Normal
39-12	10	None	15	4.5	347	44	Dead 47 hours
39-164	4	dl-methionine	40	4.2	332	401	Normal
39-164	7	Amino acids†	20	3.9	368	50	Severe intox.
39-130	11	dl-methionine	40	5.3	478	419	Normal
39-130	14	Amino acids‡	20	4.8	375	165*	Dead 40 hours
39-10	7	None	10	5.1	387	130	Moderate intox.
39-10	10	dl-methionine	40	5.1	402	343	Slight intox.

\* Twenty-four hours after ehloroform.

† l-tyrosine, l-histidine, l-alanine, l-glutamic acid.

‡ l-tryptophane, dl-phenylalanine, dl-isoleucine, l-aspartic acid, l-valine, dl-lysine.

Table 1 shows three groups of experiments in summary. The first group of 5 experiments gives further evidence that meat protein by mouth or plasma protein by vein within 24 hours before ehloroform anesthesia will give more or less protection against the ehloroform liver injury. The second group of 6 experiments shows that cystine given in various amounts and periods before the ehloroform

anesthesia does confer some protection against the chloroform liver injury. The picture may be confused because cystine in the doses given to plasma-depleted dogs may in itself cause some icterus and fatty changes in the liver cells.

The third group of 10 experiments shows that methionine has a remarkable protective action where given 4 to 24 hours before the chloroform anesthesia. In fact these protein-depleted dogs given methionine will tolerate twice the lethal chloroform anesthesia and give little or no evidence of liver injury and minimal or no clinical disturbance. Other amino-acids confer no protection.

Experiment 1 shows that nicotinic acid and lecithin added to the dogs' diet do not protect against chloroform injury. Dog 39-20 (Exp. 1) showed a typical fatal response 36 hours after 20 minutes of chloroform anesthesia. The histologic finding of 80% to 90% hyaline central necrosis was identical with that seen in the livers of dogs not receiving nicotinic acid or lecithin. This is in accord with the results of both Goldschmidt, Vars and Ravdin<sup>7</sup> and Barrett, Best, MacLean and Ridout,<sup>1</sup> who showed that choline did not materially affect the incidence or extent of liver damage from chloroform or carbon tetrachloride, respectively.

Experiments 2 and 3 (Dogs 39-16 and 38-299) show that a single large protein feeding (lean beef) can completely prevent liver injury from 20 minutes of chloroform anesthesia in the protein-depleted dog. These experiments are entirely in agreement with a similar experiment described in our previous report.<sup>13</sup>

Experiments 4 and 5 were both carried out on the same animal (Dog 38-241). In both experiments plasma protein given by vein afforded considerable but not absolute protection. As measured by clinical condition, icterus index, and drop in blood fibrinogen, the injury produced by the second anesthesia (Exp. 5) was somewhat more severe. In Experiment 4, it is interesting to note how rapidly the plasma protein level falls after the initial sudden rise following the plasma injection.

**Clinical Histories.** *Experiment 1, Dog 39-20, adult male poodle.*

Oct. 2 to 5. Fasted. Weight at end of fast 6.2 kilos. Plasma protein level 5.95 gm. per 100 cc. Red cell hematocrit 51%.

Oct. 6 to Dec. 2. Fed daily 135 gm. of low protein diet with supplement of 10 gm. beef, 25 mg. nicotinic acid, and 150 I. U. thiamine daily. Ate an average of 80% to 90% daily. Plasma protein level, Nov. 16, 4.68 gm. per 100 cc. Weight 4.3 kilos. Dec. 3, ate 60% diet.

Dec. 4. Ate 5 gm. lecithin with 50% of diet.

Dec. 5. Ate 5 gm. lecithin with 90% of diet.

Dec. 6. Ate about 50% of diet containing 10 gm. lecithin.

Dec. 7. Fasted. Weight 4.2 kilos.

Dec. 8. Red cell hematocrit 41%. Plasma protein level 5.2 gm. per 100 cc. Fibrinogen 373 mg. per 100 cc. *Chloroform anesthesia 20 minutes.* Ate very little of food offered.

Dec. 9. Dog very ill. Icterus index 18. Fibrinogen 63 mg. per 100 cc. Semicomatose at 6 P.M.

Dec. 10. Dog found dead. *Autopsy* revealed a friable liver with lobules showing conspicuous central congestion. Microscopically, there was practically complete disappearance of normal liver tissue with about 80% to 90% central hyaline necrosis.

*Experiment 2, Dog 39-16, female Spitz.*

Aug. 5. Weight 7.3 kilos. Started daily low protein diet of 135 gm. with 5 gm. fresh pork liver, 1 gm. yeast powder and 150 I. U. thiamine. Eaten 100% unless otherwise stated. Plasma protein level 6.24 gm. per 100 cc.

Sept. 5. Plasma protein level 5.03 gm. per 100 cc.

Sept. 18. Plasma protein level 4.58 gm. per 100 cc. Weight 7.2 kilos.

Sept. 23. Ate 1 pound of lean beef.

Sept. 24. Fasted.

Sept. 25. Plasma protein level 5.28 gm. per 100 cc.—rise due to meat feeding. *Chloroform anesthesia 20 minutes.* Ate only 20% of diet in P.M.

Sept. 26. Dog in good condition, bright and lively. Ate 80% of diet. Plasma shows no jaundice.

Sept. 27. Dog in excellent condition. Ate 100% diet.

Sept. 28. Dog normal. Returned to kennels (see Exp. 6 below).

*Experiment 3, Dog 38-299, female bull mongrel.*

Aug. 2. Plasma protein level 5.67 gm. per 100 cc. Started daily low protein diet of 135 gm. plus daily supplement of 1 gm. yeast powder, 150 I. U. thiamine and 5 gm. fresh pork liver. Weight 8.2 kilos. Diet eaten 100% unless otherwise stated.

Aug. 23. Plasma protein level 4.97 gm. per 100 cc.

Sept. 11. Plasma protein level 4.90 gm. per 100 cc.

Sept. 18. Plasma protein level 4.49 gm. per 100 cc. Weight 8 kilos.

Sept. 19. Ate 460 gm. lean beef.

Sept. 20. Fasted. Weight 8.2 kilos.

Sept. 21. Plasma protein level 5.28 gm. per 100 cc.—note rise due to meat feeding. *Chloroform anesthesia 20 minutes.* Ate regular diet fed 2 hours after anesthesia.

Sept. 22. Plasma protein level 5.18 gm. per 100 cc. Plasma shows no jaundice. Ate 60% of diet. Dog in very good condition.

Sept. 23. Dog normal. Ate 100% diet. Sept. 25, returned to kennels.

*Experiment 4, Dog. 38-241, adult female hound mongrel.*

Aug. 6. Placed on low protein diet, 165 gm., plus 5 gm. fresh pork liver, 1 gm. yeast powder and 150 I. U. thiamine daily. Plasma protein level 6.74 gm. per 100 cc. Weight 12.2 kilos.

Sept. 11. Plasma protein level 4.89 gm. per 100 cc. Weight 11.3 kilos.

Sept. 18. Plasma protein level 5.03 gm. per 100 cc. Weight 11.3 kilos.

Sept. 28. Plasma protein level 5.17 gm. per 100 cc. In 2 intravenous injections received a total of 270 cc. of citrated plasma containing a total of 16.4 gm. of plasma protein. Weight 10.4 kilos.

Sept. 29. Fasted.

Sept. 30. Plasma protein level 6.30 gm. per 100 cc.—note rise due to plasma injections. *Chloroform anesthesia 20 minutes.* Ate 100% diet in P.M.

Oct. 1. Plasma protein level 6 gm. per 100 cc. Icterus index 7. Appears slightly ill but is moderately active. Ate about 65% of diet.

Oct. 2. Dog still somewhat ill, but active. Icterus index 8. Ate about 75% of diet.

Oct. 3. Plasma protein level 5.33 gm. per 100 cc. Fibrinogen 349 mg. per 100 cc. Icterus index 9. Ate about 50% of diet.

Oct. 4. Condition much better. Icterus index 5. Ate about 50% of diet.

Oct. 5. Dog normal. Weight 10.5 kilos—low protein diet continues.

*Experiment 5, Dog 38-241, continued from Experiment 4.*

Oct. 16. Plasma protein level 4.81 gm. per 100 cc. Liver supplement to daily diet increased to 15 gm. Weight 10 kilos.

Oct. 27. Replaced liver supplement with equal amount of beef daily.

Nov. 16. Plasma protein level 4.67 gm. per 100 cc.

Nov. 22. Plasma protein level 4.71 gm. per 100 cc. Since Nov. 2 has eaten only an average of 40% to 50% of diet. Received intravenously 140 cc. of citrated plasma containing 8.4 gm. of plasma protein.

Nov. 23. Received intravenously 220 cc. of citrated plasma containing 13 gm. of plasma protein. Fasted.

Nov. 24. *Chloroform anesthesia 20 minutes.* Fibrinogen 373 mg. per 100 cc. Diet practically untouched in P.M.

Nov. 25. Condition good; fed about 60% of diet by stomach tube. Icterus index 13. Fibrinogen 316 mg. per 100 cc. Slight intoxication.

Nov. 26. Condition good. Refuses diet. Plasma protein level 5.96 gm. per 100 cc. Fibrinogen 205 mg. per 100 cc. Icterus index 17.

Nov. 27. Ate about 40% of diet. Condition good. Nov. 28, ate about 60% of diet.

Nov. 29. Fibrinogen 205 mg. per 100 cc. Icterus index 3. Condition normal. Weight 8.2 kilos. Returned to kennels.

TABLE 2.—CYSTINE PROTECTS AGAINST CHLOROFORM POISONING.

Hours before or after chloroform.	Plasma protein, gm. per 100 cc.	Fibrinogen, mg. per 100 cc.	Icterus index.	Food consumed, %.	Clinical condition.
<i>Experiment 6. (Dog 39-16.) Low-protein diet for 11 weeks.</i>					
0	4.24	177	1	Fast	Normal
(25 minutes chloroform anesthesia preceded by cystine supplements for 12 days.)					
24	4.15	157	8	0	Slight intoxication
48	..	129	9	10	Good
72	..	123	5	15	Very good
120	3.70	168	1	70	Normal
<i>Experiment 7. (Dog 38-169.) Low-protein diet for 6 weeks.</i>					
0	5.00	235	6	Fast	Normal
(27 minutes chloroform anesthesia preceded by cystine supplements for 4 days.)					
24	5.14	330	5	100	Normal
48	5.14	260	2	100	Normal
72	..	217	2	100	Normal
96	..	221	1	100	Normal
120	5.02	278	1	100	Normal

Experiments 6, 7 (Table 2), 8, and 10 indicate that *cystine* supplements to the low protein diet (and in some instances cysteine intravenously) protected the protein-depleted dogs from the effects of chloroform anesthetics which were sufficiently prolonged to be fatal in unprotected animals. In connection with the use of cystine as a specific protective agent, it was noted that cystine supplements greater than a few grams would often cause jaundice with a considerable icterus index before anesthesia. It is known that under certain conditions of low or incomplete protein intake cystine will cause a

considerable increase in liver fat.<sup>17</sup> Just how this fatty change in the liver could cause jaundice in the protein-depleted dog we do not know, but it suggests impaired liver function. (In several normal dogs with adequate protein intake not included in this report, equally large doses of cystine failed to cause jaundice.) Despite the fact that jaundice was present in a number of these dogs (Exps. 6, 7, and 9) before anesthesia, these animals survived a lethal chloroform anesthesia. On the basis of clinical condition and decrease in blood fibrinogen, liver injury was not very severe in any of these experiments.

Experiments 9 and 11 were done on dogs previously protected by cystine from doses of chloroform which would have been fatal to unprotected animals. In Experiments 9 and 11 Dogs 38-340 and 38-338, given 40 minutes of chloroform anesthesia (twice the lethal dose) died on the fourth day after anesthesia, but these experiments are complicated by factors which probably favored the chloroform liver injury. As a result of the cystine administration both dogs had considerable jaundice before the anesthesia was given. In Dog 38-340 there were large abscesses at the site of each subcutaneous injection of cystine and a considerable amount of cystine remained unabsorbed. Dog 38-338 was fasted for 48 hours instead of 24 hours before the anesthesia which would render the dog still more susceptible to chloroform poisoning. Despite these facts microscopic examination of the livers of both dogs revealed only a very occasional necrotic liver cell, although the hepatic parenchyma showed extensive fatty change. This is in striking contrast to the very extensive hyaline central necrosis seen in the livers of protein-depleted dogs which died as a result of only 15 to 20 minutes of chloroform anesthesia.

**Clinical Histories.** *Experiment 6, Dog 39-16, continued from Experiment 2 (Table 2).* Diet is same as in Experiment 2, plus daily supplement of 10 gm. beef instead of liver.

Nov. 16. Plasma protein level 5.03 gm. per 100 cc. Weight 7.5 kilos.

Nov. 22 and 23. Ate only 50% daily diet plus 2 gm. cystine.

Nov. 24 to 26. Ate only 35% of diet daily plus 2 gm. cystine.

Nov. 27 to 29. Ate 30% of diet daily.

Nov. 30. Fed 70% of diet by stomach tube plus 2 gm. cystine.

Dec. 1 and 2. Beef supplement increased to 15 gm. but ate 50% of diet daily plus 2 gm. cystine.

Dec. 3 and 4. Ate 50% of diet daily plus 5 gm. cystine.

Dec. 5. Diet plus 3 gm. cystine fed by stomach tube in two portions.

Dec. 6. Fasted. Weight 7 kilos.

Dec. 7 to 12. See Table 2.

*Experiment 7, Dog 38-169, adult male bull dog (Table 2).*

Oct. 9. Placed on low protein diet, 165 gm. daily with 1 gm. yeast powder and 10 gm. beef.

Oct. 14. Started daily supplement of 25 mg. of nicotinic acid and 150 I. U. of thiamine. Weight 8.5 kilos.

Oct. 16. Plasma protein 6.10 gm. per 100 cc. Oct. 30, plasma protein 4.79 gm. per 100 cc.

- Nov. 15. Daily diet supplemented with 2 gm. cystine.  
 Nov. 16. Daily diet supplemented with 4 gm. cystine. Plasma protein 5 gm. per 100 cc.  
 Nov. 17. Daily diet supplemented with 6 gm. cystine.  
 Nov. 18. Daily diet supplemented with 10 gm. cystine. Fibrinogen 235 mg. per 100 cc. Icterus index 0.  
 Nov. 19. Fasted. Weight 7.7 kilos.  
 Nov. 20 to 26. See Table 2.

*Experiment 8, Dog 38-340, adult female Spitz.*

- Oct. 5. Plasma protein, 5.94 gm. per 100 cc. Weight 9.3 kilos.  
 Oct. 6. Placed on low protein diet, 165 gm. daily with 1 gm. yeast powder and 15 gm. meat.  
 Oct. 14. Started daily supplement of 25 mg. nicotinic acid and 150 I. U. thiamine. Weight 9.3 kilos.  
 Oct. 15 to Nov. 6. Ate an average of 85% to 90% of diet daily. Plasma protein 5.21 gm. per 100 cc. (Nov. 6).  
 Nov. 7 to Dec. 13. Ate an average of 65% to 75% of diet. Plasma protein 4.78 gm. per 100 cc. Fibrinogen 269 mg. per 100 cc. (Dec. 13).  
 Dec. 14. Ate 3 gm. of cystine with 60% of diet.  
 Dec. 15 to 17. Ate about 35% of diet daily plus a total of 3 gm. cystine.  
 Dec. 18. Plasma protein 4.89 gm. per 100 cc. Fibrinogen 234 mg. per 100 cc.  
 Dec. 19 to 24. Ate an average of 40% of diet plus 6 gm. of cystine.  
 Dec. 25. Fasted. Fibrinogen 201 mg. per 100 cc. Icterus index 0. Weight 8.8 kilos.  
 Dec. 26. Plasma protein 5 gm. per 100 cc. Fibrinogen 223 mg. per 100 cc. Icterus index 0+. About 5 hours before anesthesia gave 1.45 gm. of cysteine plus 5 gm. glucose in 150 cc. of physiologic saline by vein. *Chloroform anesthesia 30 minutes.* Ate no food in P.M.  
 Dec. 27. Condition good. Fairly active. Fibrinogen 160 mg. per 100 cc. Icterus index 8.  
 Dec. 28. Condition good. Ate 15% of food. Icterus index 11.  
 Dec. 29. Condition better. Ate 30% of food. Fibrinogen 285 mg. per 100 cc. Icterus index 6.  
 Dec. 30 and 31. Condition normal. Ate 50% of food each day. On Dec. 31, fibrinogen 324 mg. per 100 cc. Icterus index 3.

*Experiment 9, Dog 38-340, continued from Experiment 8.*

- Jan. 3 to Jan. 14. Ate an average of 50% of diet (same as in Exp. 8). Weight, Jan. 14, 8.3 kilos.  
 Jan. 15. Plasma protein 4.94 gm. per 100 cc. Ate about 30% of diet.  
 Jan. 16. Ate about 30% of diet, rest given by stomach tube. An undetermined amount was vomited.  
 Jan. 17. Fasted. At 9 P.M. 5 gm. of cystine almost completely dissolved in 10% sodium carbonate was given subcutaneously.  
 Jan. 18. Dog somewhat ill. Severe local reaction at sites of injection. At 10 A.M. received 5 gm. cystine plus 5 gm. glucose by stomach tube of which one-fifth was vomited. Plasma protein 5.20 gm. per 100 cc. Fibrinogen 351 mg. per 100 cc. Icterus index 1. *Chloroform anesthesia 40 minutes.* Food untouched in P.M.  
 Jan. 19. Has vomited considerable mucus during night. Fibrinogen 574 mg. per 100 cc. Icterus index 7. Intravenous glucose 25 gm. in 100 cc. of saline. Vomiting continues.  
 Jan. 20. Although obviously weakened, still active and conscious. Vomiting mucus has continued through the night. Fibrinogen 648 mg. per 100 cc. (due to abscesses). Icterus index 30. Intravenous glucose 20 gm. in 125 cc. of saline and later 20 gm. in 175 cc. of saline. Vomiting continues.

Jan. 21. Condition worse. Semicomatose late in evening despite several doses of intravenous glucose. Fibrinogen 526 mg. per 100 cc. Icterus index 26.

Jan. 22. Found dead. On autopsy found two large abscesses at sites of cystine injections. Liver grossly yellowish in color. Microscopically, only a very occasional liver cell is necrotic, but the liver cells show extensive fatty change and definite icterus with brown casts in many bile canaliculi. This is not the typical picture of delayed chloroform poisoning.

*Experiment 10, Dog 38-338, male hound mongrel.*

Oct. 2 to 4. Fasted.

Oct. 5. Started low protein diet 165 gm. Supplemented daily with 25 mg. nicotinic acid, 150 I. U. thiamine and 10 gm. meat. Weight 12.2 kilos.

Oct. 16. Plasma protein 5.31 gm. per 100 cc.

Oct. 31. Plasma protein 4.88 gm. per 100 cc.

Nov. 3 and 9. Ate 50% of diet.

Nov. 11. Diet containing 10 gm. cystine untouched.

Nov. 12. Fasted except for 10 gm. cystine, 4 gm. Klim, 5 gm. glucose given by stomach tube.

Nov. 13. Repeated above mixture at 11 A.M. Plasma protein 4.68 gm. per 100 cc. Fibrinogen 355 mg. per 100 cc. Icterus index 14. *Chloroform anesthesia 20 minutes* at 3 P.M. Ate practically none of diet in P.M.

Nov. 14. Vomited mucus once. Condition fairly good. Fibrinogen 283 mg. per 100 cc. Icterus index 26. Ate practically none of diet.

Nov. 15. Condition good and fairly active but ate none of diet. Given 25 gm. glucose in 100 cc. saline by vein. Plasma protein 4.25 gm. per 100 cc. Fibrinogen 195 mg. per 100 cc. Icterus index 27.

Nov. 16. Condition good, but ate very little of diet. Fibrinogen 135 mg. per 100 cc. Icterus index 18.

Nov. 17. Condition good. Fed 50% of diet by tube; ate rest by following day. Fibrinogen 184 mg. per 100 cc. Icterus index 7.

Nov. 18. Condition normal. Ate 70% of diet. Fibrinogen 238 mg. per 100 cc. Icterus index 1.

Nov. 19. Returned to kennels. Weight 10.6 kilos.

*Experiment 11, Dog 38-338, continued from Experiment 10.*

Dec. 15 to 25. Ate an average of 65% of low protein diet, supplemented with 5 gm. lecithin and increased beef to 15 gm. daily. Weight (Dec. 15) 10.2 kilos.

Dec. 26 and 27. Ate 50% of diet daily containing 6 gm. of cystine.

Dec. 28 to 30. Ate about 25% of diet daily, containing about 4 gm. of cystine.

Dec. 31. Ate only about 10% of diet containing 0.2 gm. cystine. Icterus index 6. Jan. 1, fasted.

Jan. 2. Plasma protein 4.55 gm. per 100 cc. Fibrinogen 237 mg. per 100 cc. Icterus index 5. About 4 hours before anesthesia received intravenously a solution of 2.3 gm. cysteine hydrochloride, 1.5 gm. sodium bicarbonate and 5 gm. glucose in 150 cc. of physiologic saline. This caused dog to vomit thick mucus repeatedly for about 1 hour. *Chloroform anesthesia 40 minutes*. Ate no food in P.M.

Jan. 3. Condition fairly good. Fibrinogen 232 mg. per 100 cc. Icterus index 10. Ate no food.

Jan. 4. Obviously ill. Fibrinogen 166 mg. per 100 cc. Icterus index 11. Received 150 cc. of saline subcutaneously. Vomited mucus. Ate no food.

Jan. 5. Condition poor but still active. Received 100 cc. saline by vein and 100 cc. saline intravenously in the morning and 200 cc. saline subcutaneously in the afternoon because of intermittent vomiting. Con-



dition worse later in the day. Fibrinogen 185 mg. per 100 cc. Icterus index 14. Ate no food.

Jan. 6. Semicomatose. Plasma protein 4.27 gm. per 100 cc. Fibrinogen 185 mg. per 100 cc. Icterus index 19. Dead at 9.30 A.M. On autopsy liver was grossly saffron yellow in color and central areas of lobules only slightly accentuated. Microscopically, the liver cells in the mid-zone especially show extreme fatty degeneration. There are many pigmented phagocytes in the center of the liver lobules. Icterus is not obvious. No typical hyaline liver necrosis noted.

It is believed that *methionine* can replace cystine in any reaction of detoxication and methionine is definitely lipotropic in contrast to cystine which in certain conditions favors the deposit of fat in the liver. Therefore one might suspect that methionine would be superior to cystine as an agent protective against chloroform liver injury. In these experiments it is obvious that methionine is distinctly more effective.

**Clinical Histories.** *Experiment 12, Dog 39-157, adult female Spitz (Table 3).*

Jan. 12. Placed on low protein diet, 165 gm. with daily supplement of 15 gm. beef, 25 mg. nicotinic acid, 150 I. U. thiamine and 5 gm. lecithin. Weight 7.5 kilos.

Jan. 15. Plasma protein 6.87 gm. per 100 cc.

Jan. 16 to Feb. 14. Ate 100% of diet. Plasma protein (Feb. 3) 5.09 gm. per 100 cc.

Feb. 15 to Mar. 10. Ate an average of 80% of diet daily.

Mar. 11. Ate about 50% of diet containing a supplement of 2 gm. methionine. Rest fed by stomach tube with an additional 2 gm. methionine. Small amount vomited.

Mar. 12. Plasma protein 4.96 gm. per 100 cc. Ate 15% of diet. Fed rest with 2 gm. methionine by stomach tube. Some vomited.

Mar. 13. Fasted. Weight 7.9 kilos.

Mar. 14 to Mar. 18. Glucose 10 gm. in 100 cc. saline intravenously on 15, 16 and 17 (see Table 3).

*Experiment 13, Dog 39-157, continued from Experiment 12 (Table 3).*

Mar. 19 to Apr. 9. Ate a daily average of about 55% of same diet as in Exp. 12 with lecithin replaced by 200 mg. choline hydrochloride daily.

Apr. 10. Fasted. Weight 7.5 kilos.

Apr. 11 and 12. See Table 3.

Apr. 13. Found dead. On autopsy, the liver was uniformly reddish brown with centers of lobules markedly congested. Microscopically, there was extensive hyaline central necrosis involving about 60% to 70% of the lobule cross-section.

Table 3 shows 2 experiments which are convincing. The same protein-depleted dog given methionine by mouth and by vein before the anesthesia tolerated 40 minutes chloroform anesthesia and showed no evidence of liver injury and little or no clinical disturbance. After an interval of 4 weeks the dog was given chloroform anesthesia for 15 minutes (no methionine) which caused a typical fatal chloroform poisoning in 36 hours.

TABLE 3.—METHIONINE PROTECTS AGAINST CHLOROFORM POISONING.

Hours before or after chloroform.	Plasma protein, gm. per 100 cc.	Fibrinogen, mg. per 100 cc.	Icterus index.	Food consumed, %.	Clinical condition.
<i>Experiment 12 (Dog 39-157). Low-protein diet for 8 weeks.</i>					
0	4.96	450	0	Fast	Normal
(Chloroform anesthesia—40 minutes, preceded by methionine in diet, 2 gm. per day, for 2 days and by vein, 2 gm., 3 hours before anesthesia.)					
24	4.95	383	0	5	Good
48	4.94	421	0	5	Good
72	..	453	0	5	Good
96	..	448	0	5	Normal
120	..	438	0	40	Normal
<i>Experiment 13 (Dog 39-157). Low protein diet continued 4 weeks more. No methionine given.</i>					
2	4.83	327	0	Fast	Normal
(Chloroform anesthesia—15 minutes.)					
24	4.76	38	12	0	Intoxicated
36	Death—chloroform poisoning. Extensive liver injury.				

**Clinical Histories.** *Experiment 14, Dog 39-12, adult female hound mongrel.*

Jan. 23. Placed on diet (165 gm. daily), supplemented daily with 10 gm. beef, 25 mg. nicotinic acid, 200 mg. choline hydrochloride, 150 I. U. of thiamine chloride. Plasma protein 5.90 gm. per 100 cc. Weight 11.1 kilos.

Feb. 27. Plasma protein 4.78 gm. per 100 cc. Weight 11.1 kilos.

Mar. 5 and 6. Supplemented diet with 2 gm. methionine each day.

Mar. 7. Fasted except for 2 gm. of methionine plus 3 gm. glucose given by stomach tube.

Mar. 8. Before anesthesia, plasma protein 4.45 gm. per 100 cc. Fibrinogen 264 mg. per 100 cc. Icterus index 0. One hour before 40 minutes of chloroform anesthesia the dog was given 2 gm. methionine plus 3 gm. glucose by stomach tube. Fed 100% of diet plus 1 gm. methionine by stomach tube in P.M.

Mar. 9. Condition good although dog appears slightly ill. Fed about 75% of diet by stomach tube. Fibrinogen 314 mg. per 100 cc. Icterus index 0.

Mar. 10. Condition good. Ate 100% of diet. Fibrinogen 222 mg. per 100 cc. Icterus index 1.

Mar. 11. Condition normal. Ate 100% of diet. Plasma protein 4.22 gm. per 100 cc. Fibrinogen 181 mg. per 100 cc. Icterus index 0.

Mar. 12. Condition normal. Plasma protein 4.49 gm. per 100 cc. Fibrinogen 223 mg. per 100 cc. Icterus index 0.

*Experiment 15, Dog 39-12, continued from Experiment 14.*

Mar. 13 to Apr. 7. Continued to eat 100% of low protein diet of Exp. 14.

Apr. 8. Fasted. Weight 11.6 kilos.

Apr. 9. Plasma protein 4.47 gm. per 100 cc. Fibrinogen 347 mg. per 100 cc. Icterus index 0. Chloroform anesthesia 15 minutes. Shortly after recovery, ate 100% of regular diet.

Apr. 10. Obviously ill and inactive. Vomited bile-stained mucus several times. Plasma protein 4.29 gm. per 100 cc. Fibrinogen 58 mg. per 100 cc. Icterus index 9. Received 250 cc. of 5% glucose in saline subcutaneously.

Apr. 11. Dead at 11 A.M. Shortly before death, fibrinogen 44 mg. per 100 cc. Icterus index 21. At autopsy the liver lobules grossly showed deep red central areas. Microscopically, there was extensive central hyaline necrosis corresponding to about 50% to 60% of the lobule cross-sectional areas.

Experiments 14 and 15 are very like those in Table 3. Again, methionine given by stomach tube on several days before the chloroform anesthesia protects the dog against 40 minutes of chloroform and the dog shows no evidence of liver injury and only slight clinical intoxication. After an interval of 4 weeks the dog was given 15 minutes of chloroform anesthesia (no methionine) which caused a fatal chloroform poisoning in 48 hours.

**Clinical Histories.** *Experiment 16, Dog 39-164, adult female Boston bull (Table 4).*

Mar. 26 to 31. Fasted.

Apr. 1. Placed on low protein diet, 165 gm. daily with daily supplements of 15 gm. beef, 150 I. U. of thiamine, 25 mg. nicotinic acid, 200 mg. choline hydrochloride. Weight 8.3 kilos. Plasma protein 5.56 gm. per 100 cc.

Apr. 2 to 22. Ate 100% of diet. Plasma protein (April 17) 4.31 gm. per 100 cc.

Apr. 23 and 24. Received diet supplement of 2 gm. methionine each day.

Apr. 25. Fasted. Weight 8.4 kilos.

Apr. 26 to 29. Received 2 gm. methionine with food on April 26 (see Table 4).

*Experiment 17, Dog 39-164, continued from Experiment 16 (Table 4).*

May 1 to 13. Ate an average of 80% of diet as given in Experiment 16. Weight (May 13) 6.8 kilos.

May 14. Fasted except for amino acids supplement: 1 gm. l-tyrosine, 1 gm. l-alanine, 1 gm. l-histidine hydrochloride, 1 gm. l-glutamic acid and 5 gm. glucose in 100 cc. of saline by stomach tube.

May 15. Repeated amino-acid mixture by stomach tube at 9 A.M. Plasma protein 3.92 gm. per 100 cc. Fibrinogen 368 mg. per 100 cc. Icterus index 0. *Chloroform anesthesia 20 minutes* at noon. Ate 100% of diet. Some vomited later.

May 16. Condition fairly good. Plasma protein 4.27 gm. per 100 cc. Fibrinogen 310 mg. per 100 cc. Icterus index 8. Refused food. At 8 P.M. condition poor, conjunctiva extremely congested. Fibrinogen 156 mg. per 100 cc. Icterus index 13. Received 10 gm. glucose in 100 cc. saline. Ate no food.

May 17. Condition very poor. Very weak. Chemosis and congestion of conjunctiva. Hemorrhage anterior chambers of both eyes. Slow oozing of blood from previously inconspicuous sores on both front legs. Fibrinogen 50 mg. per 100 cc. Icterus index 15. Ate no food. Almost fatal intoxication and bleeding.

May 18. Condition poor, but appears brighter. Very weak. Improved after receiving intravenously 15 gm. glucose in 100 cc. saline. Fibrinogen 109 mg. per 100 cc. Icterus index 25. Ate no food.

May 19. Slightly improved. Extreme weakness somewhat relieved by 15 gm. glucose in 100 cc. saline given intravenously. Fibrinogen 168 mg. per 100 cc. Icterus index 22. Ate no food.

May 20. Condition much better. Still weak, but ate some of diet. Plasma protein 3.55 gm. per 100 cc. Fibrinogen 197 mg. per 100 cc. Icterus index 7.

May 21. Condition much better. Ate about 50% of food.

May 22. Condition normal. Fibrinogen 275 mg. per 100 cc. Icterus index 1. Returned to kennels.

Table 4 shows again the powerful protective action of methionine and in contrast the neutral effect of a group of non-sulphur containing

amino-acids. The dog when given methionine by mouth and by vein before the anesthesia tolerates 40 minutes of chloroform anesthesia with little or no clinical disturbance and no signs of liver injury. After 3 weeks the dog is given a mixture of amino-acids as control for the methionine and 20 minutes chloroform anesthesia. This caused a very severe liver injury with high icterus index and very low fibrinogen levels. The dog was severely intoxicated and bled from skin ulcers and into the chambers of both eyes. It appeared certain that death would follow but recovery took place within a week.

TABLE 4.—METHIONINE PROTECTS AGAINST CHLOROFORM POISONING. TYROSINE, ALANINE, HISTIDINE AND GLUTAMIC ACID DO NOT PROTECT.

Hours before or after chloroform.	Plasma protein, gm. per 100 cc.	Fibrinogen, mg. per 100 cc.	Icterus index.	Food consumed, %.	Clinical condition.
<i>Experiment 16 (Dog 39-164). Low-protein diet for 4 weeks.</i>					
0	4.23	332	0	Fast	Normal
(Chloroform anesthesia—40 minutes, preceded by methionine, 2 gm. in diet for each of 2 days, and by vein, 2 gm. shortly before anesthesia.)					
24	4.44	352	1	100	Good
48	4.56	401	1	35	Good
72	4.45	479	0	30	Normal
96	..	..	0	50	Normal
<i>Experiment 17 (Dog 39-164). Low-protein diet continued for 3 weeks.</i>					
0	3.92	368	0	Fast	Normal
(Chloroform anesthesia—20 minutes, preceded by tyrosine, alanine, histidine, and glutamic acid given 24 and 3 hours before anesthesia.)					
24	4.27	310	8	100	Intoxication
48	..	50	15	0	Severe intoxication
72	..	109	25	0	Poor
96	3.63	168	22	0	Improved
120	3.55	..	7	0	Fairly good

**Clinical Histories.** *Experiment 18, Dog 39-130, adult male mongrel (Table 5) (like Table 4).*

Jan. 15. Placed on low protein diet (same as Dog 39-164, Exps. 16 and 17). Plasma protein 7.23 gm. per 100 cc. Weight 13.5 kilos.

Feb. 27. Plasma protein 5.40 gm. per 100 cc. Weight 12.4 kilos.

Apr. 17. Plasma protein 5.09 gm. per 100 cc. Weight 11.8 kilos.

Apr. 29. Ate 40% of diet. Apr. 30, fasted.

May 1 to 4. See Table 5.

May 6. Condition normal. Plasma protein 5.40 gm. per 100 cc. Fibrinogen 425 mg. per 100 cc. Icterus index 0. Ate 50% of diet. Weight 11.3 kilos.

*Experiment 19, Dog 39-130, continued from Experiment 18 (Table 5).*

May 7 to 22. Ate a daily average of 50% to 60% of same diet used in Exp. 18.

May 23. Fasted except for amino-acid mixture of 1 gm. l-tryptophane, 1 gm. dl-phenylalanine, 1 gm. dl-isoleucine, 1 gm. l-aspartic acid, 1 gm. l-valine, 1 gm. dl-lysine dihydrochloride, and 5 gm. glucose in 100 cc. saline, given by stomach tube at 4 P.M.

May 24. Gave above amino-acid mixture by stomach tube at 9.45 A.M. Plasma protein 4.80 gm. per 100 cc. Fibrinogen 375 mg. per 100 cc. Icterus

index 0. *Chloroform anesthesia 20 minutes* at 1 P.M. Ate about 10% of diet in P.M. Vomited once during night.

May 25. Inactive and ill but bright. At 9 A.M. fibrinogen 188 mg. per 100 cc. Icterus index 7. At 1 P.M. fibrinogen 165 mg. per 100 cc. Icterus index 9. Ate no food.

May 26. Found dead. Vomited several times during night. Icterus index approximately 15 (blood taken at autopsy). Autopsy revealed a grossly yellowish brown liver with reddish hemorrhagic central areas standing out. Microscopically, there was extensive central hyaline necrosis corresponding to 70% to 80% of the lobules in cross-section.

TABLE 5.—METHIONINE PROTECTS AGAINST CHLOROFORM POISONING. TRYPTOPHANE, PHENYLALANINE, ISOLEUCINE, ASPARTIC ACID, VALINE AND LYSINE DO NOT PROTECT.

Hours before Plasma protein, or after chloroform.	gm. per 100 cc.	Fibrinogen, mg. per 100 cc.	Icterus index.	Food consumed, %.	Clinical condition.
<i>Experiment 18 (Dog 39-130). Low-protein diet for 11 weeks.</i>					
0	5.39	478	0	Fast	Normal
(Chloroform anesthesia—40 minutes, preceded by methionine intravenously, 2.5 gm. 5 hours before and 2.3 gm. 2 hours before.)					
24	5.35	440	0	60	Good
48	5.21	419	0	15	Good
72	5.19	403	0	85	Normal
120	5.40	425	0	50	Normal
<i>Experiment 19 (Dog 39-130). Low-protein diet continued for 3 weeks.</i>					
0	4.80	375	0	Fast	Normal
(Chloroform anesthesia—20 minutes, preceded by amino acid mixture 21 hours and 4 hours before, by stomach tube.)					
24	..	165	9	10	Intoxicated
44	Death—chloroform poisoning.				

Table 5 shows that a total of 4.8 gm. methionine given intravenously 5 and 2 hours before anesthesia will give complete protection against 40 minutes of chloroform anesthesia. The control again shows that non-sulphur containing amino-acids confer no protection and fatal chloroform poisoning follows 20 minutes anesthesia.

**Clinical Histories.** *Experiment 20, Dog 39-10, adult female shepherd mongrel (Table 6),*

Jan. 29. Started diet. Identical with that of Dog 39-12 in Exp. 15. Plasma protein 6.60 gm. per 100 cc. Weight 8.9 kilos.

Jan. 30 to Mar. 12. Ate an average of 90% of diet. Plasma protein (Mar. 12) 5.40 gm. per 100 cc. Weight 9 kilos.

Mar. 13 to Apr. 16. Ate 50% to 60% of diet.

Apr. 17. Plasma protein 5.22 gm. per 100 cc. Weight 9.1 kilos.

Apr. 18. Fasted.

Apr. 19 to 23. See Table 6.

*Experiment 21, Dog 39-10, continued from Experiment 20 (Table 6).*

Apr. 24 to May 9. Ate an average of 50% of diet.

May 10 to 14. See Table 6.

May 15. Condition normal. Returned to kennels. Weight 9.1 kilos.

Table 6 shows a reversal of the sequence to control some factors related to repeated insults and liver cell regeneration as shown by

MacNider.<sup>10</sup> The first chloroform injury to the protein-depleted dog is caused by only 10 minutes anesthesia (about one-half to two-thirds the lethal exposure). This caused definite intoxication and evidence of some liver injury. After an interval of 3 weeks, which is adequate for liver repair, the dog was given methionine intravenously 20 and 2 hours before anesthesia. Chloroform anesthesia of 40 minutes then caused not the slightest clinical disturbance and no signs of liver injury. This is evidence again that methionine confers a strong resistance against chloroform liver injury.

TABLE 6.—METHIONINE PROTECTS AGAINST CHLOROFORM POISONING.

Hours before or after chloroform.	Plasma protein, gm. per 100 cc.	Fibrinogen, mg. per 100 cc.	Icterus index.	Food consumed, %.	Clinical condition.
<i>Experiment 20 (Dog 39-10). Low-protein diet for 7 weeks.</i>					
0	5.05	387	0	Fast	Normal
	(Chloroform anesthesia—10 minutes. No methionine.)				
24	4.84	177	1.5	50	Slight intoxication
48	..	130	4	20	Slight intoxication
72	4.60	164	1	30	Good
96	..	205	0	50	Very good
<i>Experiment 21 (Dog 39-10). Low-protein diet for additional 3 weeks.</i>					
0	5.12	402	0	Fast	Normal
	(Chloroform anesthesia—40 minutes, preceded by 5 gm. methionine intravenously in two portions, 20 and 2 hours before chloroform.)				
24	5.00	377	1	0	Excellent
48	..	343	0	25	Excellent
72	..	321	0	50	Excellent
96	..	...	...	50	Normal

**Discussion.** Perfect experiments in physiology or pathology are rare indeed and when encountered deserve comment. The experiments in Table 5 approach this goal of perfection. We note that this protein-depleted dog given methionine by vein 5 and 2 hours before chloroform anesthesia tolerated 40 minutes (twice the lethal period) and showed no evidence of liver injury or clinical intoxication. After an interval of 3 weeks a mixture of amino-acids (other than methionine or cystine) were given as controls before anesthesia. In this experiment 20 minutes caused a fatal chloroform poisoning with death in 44 hours and the typical picture of massive central liver necrosis. Table 6 is almost as satisfactory and shows the primary injury due to 10 minutes chloroform. After 3 weeks the dog was given methionine and subjected to 4 times the anesthesia period (40 minutes) which caused no clinical disturbance and no signs of liver injury.

Two perennial questions invariably arise in any discussion of chloroform poisoning. What mechanism accounts for the liver cell necrosis and why is the liver necrosis or injury (fat) produced by chloroform and other organic halogenated compounds invariably centrally located? Many inadequate answers to these questions

will be found in the literature and our readers may not agree that our answer to these questions is correct or even approximately so, yet we submit a thesis which is in harmony with the experiments given above.

We suggest that protein protects animals from the toxic effects of chloroform anesthesia by making available methionine and cystine. Both casein, which was found so effective<sup>7</sup> in protecting rats, and beef muscle and plasma protein used by us, are good sources of methionine or cystine. The evidence strongly suggests that these amino-acids are concerned with the specific detoxication of chloroform to form a conjugation product similar to the mercapturic acids already described in the literature. (In preliminary experiments, methods which have resulted in the isolation of known mercapturic acids have thus far failed to yield any compound which might be a similar detoxication product for chloroform.) Thus it is suggested that protein-depleted dogs are very susceptible to liver injury by chloroform as a direct consequence of the relatively limited amount of methionine- and cystine-containing liver protein. Briefly put, for the chloroform experiment the protein-depleted dog is probably a cystine- and methionine-depleted dog.

An alternative but to us a less attractive theory would attribute to methionine and (or) cystine a key rôle in the construction of new liver protein or reconstruction of damaged liver cell protein. Moreover it will be recalled that experiments<sup>11</sup> with plasma-depleted dogs give evidence that cystine and methionine are almost key amino-acids when it comes to the production of much new plasma protein. This, however, does not prove that these two amino-acids are key acids for the building of new liver protein. It is difficult to visualize this extensive production of new liver protein containing much of the methionine given 3 to 5 hours before the chloroform anesthesia, although one perhaps could imagine these S-amino-acid groups being incorporated in large protein molecules in a very short time.

The results of the above experiments show that methionine is much more effective than cystine. Although both amino-acids can be converted to mercapturic acids to equivalent degrees, it is conceivable that the amounts of cystine (and cysteine) given caused a considerable increase in liver fat, especially since these animals may not have been getting adequate choline. The observations of Tucker and Eckstein,<sup>17</sup> Beeston and Channon<sup>2</sup> and others certainly indicate that cystine can cause relatively large increases in liver fat which might impair liver function to some extent. Certainly the jaundice in most of the cystine-fed animals is an indication of some disturbance in liver function. In spite of this confusing reaction, it is significant that cystine was unquestionably of protective value.

As a control we have tested a variety of amino-acids (see Tables 4 and 5) under identical conditions. Alone (glycine) or in various combinations, the non-sulphur amino-acids seem to be inert and confer no protection against chloroform poisoning.

It is well known that the function of a number of enzymes as well as glutathione is intimately associated with the presence of  $-SH$  groups. It is also known that certain halogenated compounds conjugate very readily with  $-SH$  groups<sup>12,15</sup> and thus completely eliminate their ability to function (for example, in an oxidation-reduction system). Binet, Weller and Gondard<sup>3</sup> have described a decrease in the glutathione content of the liver following chloroform given *per os*. Other workers<sup>9</sup> have shown that feeding cysteine increases the liver glutathione content. It is conceivable that injury or necrosis of liver cells may result from more or less extensive conjugation of chloroform with  $-SH$  groups of glutathione and vital enzyme systems. Where the number of such inactivated groups per cell is relatively small (large reserve protein stores, or short anesthesia, or increased cysteine available), then liver cell injury will be prevented.

Just exactly what happens to cystine or methionine when administered to a protein-depleted animal on a low protein diet we are unprepared to say. Nielsen, Gerber and Corley<sup>14</sup> have demonstrated the retention in the dog of the nitrogen of a cystine supplement to a low protein diet, and Stekol<sup>16a</sup> has shown that l-cystine and dl-methionine sulphur is retained under similar conditions. It is possible that the liver of the protein-depleted dog retains a relatively large amount of these amino-acids by increasing the S-amino-acid content of liver protein already present, by increasing the glutathione content, or in some other way. In any case the S-containing amino-acid would become rapidly available for conjugation purposes since (in Exp. 18, Dog 39-130, Table 5) methionine was given only 5 hours before 40 minutes of chloroform anesthesia and no perceptible liver injury was shown. Experiments are now in progress to demonstrate to what extent sulphur-containing amino-acids are incorporated by or retained in liver tissue following the feeding of cystine or methionine to protein-depleted animals on a low protein diet.

If the action of chloroform and certain other organic compounds on the liver can be interpreted in terms of specific conjugation with and inhibition of free  $-SH$  groups, then one might suspect that the fatty change and necrosis most commonly seen as a result of the action of these materials is central because of the relatively lower oxygen tensions at the centers of the liver lobules. Furthermore, the work of Blalock and Mason<sup>4</sup> indicates that in contrast to venous blood from other organs, venous blood from the liver contains considerably less oxygen. With this rapid fall in oxygen tension within the liver lobule and concomitant fall in oxidation reduction potential,



it is logical to assume that the number of free sulphydryl groups would increase and disulphide groups decrease from the periphery to the center of the liver lobule: hence central cell necrosis. In this connection it is interesting to note that Goldschmidt, Ravdin and Lucké<sup>6</sup> observed a decrease in the extent of liver damage when the chloroform used for anesthesia was volatilized with oxygen.

No adequate explanation has ever been given to indicate why chloroform has a specific affinity for liver cells rather than for other gland cells rich in ferments (for example the pancreas) nor have we any explanation to offer.

**Summary.** Methionine and to a less extent cystine given by mouth or by vein 24 to 5 hours before anesthesia give a remarkable and almost complete protection to the protein-depleted dog against chloroform poisoning.

Other non-sulphur-containing amino-acids alone or in various combinations as tested convey no protection against chloroform poisoning in similar experiments.

A single large beef feeding or plasma protein by vein 24 to 48 hours before anesthesia will likewise protect against chloroform poisoning and it is suggested that the sulphur-containing amino-acids are responsible.

The protein-depleted dog will succumb to 15 to 20 minutes light chloroform anesthesia and show extensive liver necrosis. The dog protected by methionine will tolerate 40 minutes chloroform anesthesia with little or no clinical disturbance and no evidence of liver injury.

It is suggested that the sulphydryl groups combine with chloroform. This combination may inactivate enzyme systems and thus bring about cell death unless there is an adequate reserve of cystine and methionine.

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## CLINICAL STUDIES OF EXPERIMENTAL HUMAN VITAMIN B COMPLEX DEFICIENCY.

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CLAIMS have recently been made for the efficacy of members of the vitamin B complex in a variety of clinical conditions. Many of them are based on uncontrolled observations, and their validity is therefore difficult to assess. It is our belief that only when the environment has been carefully controlled and coëxisting deficiencies eliminated can a reliable estimate be made of the rôle of vitamin B factors in clinical medicine. In accordance with this belief one of us in 1933<sup>3a</sup> studied the changes which took place in a healthy volunteer who for approximately 1 year consumed a diet deficient only in the vitamin B complex. This experiment enabled us to describe clinical signs and alterations in function attributable to vitamin B complex deficiency. An extension of these observations seemed desirable and, because group experiments in this field are relatively unsatisfactory due to the unusual coöperation required of the subjects, it was decided to use the same volunteer and to repeat the experiment in its essentials, employing more detailed methods of study and testing the effects of components of the vitamin B complex unknown in 1933. The present report therefore deals with the results of repeated clinical examinations and of studies of cardiovascular, neurologic and hematopoietic functions and of alterations in the Roentgen appearance of the gastro-intestinal tract made while the subject consumed the deficient diet alone and also following the addition to the diet of thiamin, of riboflavin and of brewer's yeast. The studies made at this time on fluid balance, body weight, nitrogen excretion, carbohydrate metabolism and response to insulin have been reported elsewhere.<sup>4</sup>

**Methods.** The study was made in the metabolic ward of the Hospital of the University of Pennsylvania from February 25 to June 25, 1938. During that time the subject, a healthy woman aged 60, voluntarily consumed a constant daily quantity of a weighed diet. As described elsewhere<sup>4</sup> the diet

was adequate in protein, fat, carbohydrate and total calories and was supplemented with optimal amounts of vitamins A, C and D and of iron and calcium. Thiamin was present in approximately one-third the individual's minimal requirement as calculated by the Cowgill formula.<sup>1</sup> It was assumed that other members of the vitamin B complex were correspondingly reduced. Daily fluid intake was constant. The experiment was divided into five consecutive periods: 1, the first week on the deficient diet which was regarded as the control period; 2, the subsequent 8 weeks during which time signs of deficiency developed; 3, a period of 18 days when thiamin hydrochloride\* alone was added to the diet in doses ranging from 20 to 120 mg. daily; 4, 20 days during which riboflavin, 6 mg. daily, was administered in addition to thiamin; 5, a final 18 days when brewer's yeast† alone, 42 gm. daily, was given. This period was shorter than desired, due to unavoidable circumstances, so that the effects of this therapeutic agent were evident but probably not maximal before it was necessary for the subject to leave the hospital.

The subject was examined daily and a record kept of symptoms and physical signs. Pulse and blood pressure readings were made 3 times daily under basal conditions. Electrocardiograms and orthodiagrams were made at the beginning and end of each period. Roentgen examination of the gastrointestinal tract was made at the end of each period. Following administration of a standard barium meal to the fasting subject, observations were carried out at hourly intervals for 4 to 5 hours. Neurologic examination and determination of electrical irritability of the peripheral nerves, according to the method previously described,<sup>6</sup> were made at the end of each period. The following studies of the blood were made frequently: erythrocyte counts in triplicate, using pipettes certified by the U. S. Bureau of Standards; hematocrit determinations in triplicate, using Wintrobe tubes, and estimations of hemoglobin percentage by the Sahli method. Mean corpuscular volume and mean corpuscular hemoglobin were calculated in the usual fashion.<sup>13</sup> Morphologic changes in the blood were observed from smears prepared with Wright's stain.

**Results.** 1. **CARDIOVASCULAR STUDIES.** After 5 weeks on the experimental diet, the subject complained of dyspnea and palpitation (Table 1). She also experienced sharp pain in the left anterior chest from time to time. Occasionally it occurred during exertion, but its location and character were not typically anginal.

On physical examination short periods of tachycardia were observed which lasted a few hours. Later they became more frequent, until, during the last 5 days of deficiency, the resting pulse rate was never below 90 and frequently was as high as 108. The average of 100 (Fig. 1) represented an increase of 17 beats per minute over the control period. With the patient at rest the pulse varied abruptly both in rate and strength. At times a soft systolic murmur was audible over the aortic area. No significant changes in resting blood pressure, electrocardiogram or orthodiagram were observed.†

All the cardiovascular symptoms and physical signs regressed

\* This material (as Betabion) and riboflavin were supplied through the courtesy of Merck & Co.

† The brewer's yeast was kindly supplied by Dr. L. J. Harris of the Harris Laboratories, Tuckahoe, N. Y., as "Brewer's Yeast-Harris Medicinal Powder."

‡ We are indebted to Dr. F. C. Wood for the electrocardiograms and orthodiagrams and for their interpretations.

promptly after the administration of thiamin. At the end of 1 week the average resting pulse was 90, by the end of the second week it was normal and remained so thereafter. Variation in intensity of the pulse was not again observed nor was the aortic murmur heard. Dyspnea and precordial distress disappeared.

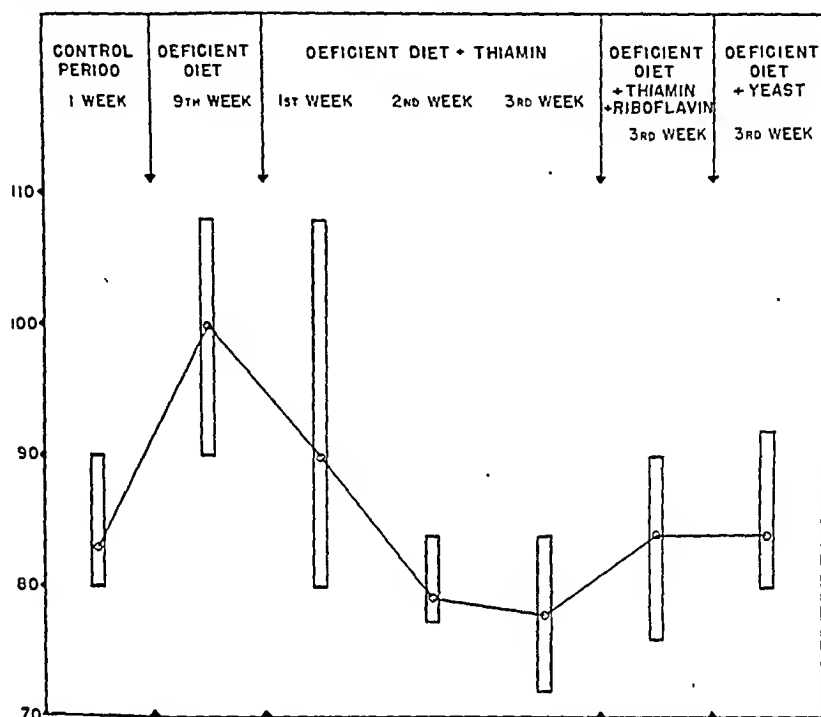


FIG. 1.—Changes in the resting pulse rate. Columns indicate the maximum variations in each period.

TABLE 1.—CLINICAL OBSERVATIONS ON A VITAMIN B DEFICIENT DIET.

Clinical observations.	Vitamin B deficient diet.			Deficient diet + thiamin.	Deficient diet + thiamin, + riboflavin.	Deficient diet + yeast.
	1st week.	5th week.	9th week.			
<i>Symptoms:</i>						
Easy fatigue . . . . .	0	++	++++	+	++	0
Anorexia . . . . .	+	+++	++++	+	++	+
Cardiac . . . . .	0	+	+++	0	0	0
Gastro-intestinal . . . .	0	++	+++	+++	+++	0
Neurologic . . . . .	0	+	++	0	0	0
Mental . . . . .	0	+	++++	++	++	0
<i>Physical signs and special observations:</i>						
Change in appearance . .	0	+	++++	++	++	0
Edema . . . . .	+	++	++	++	++	+
Increased pulse rate . . .	0	+	++	0	0	0
G.I. Roentgen changes . .	0	..	++	++	++	0
Neurologic signs . . . .	0	+	++	0	0	0
Blood changes . . . . .	0	0	+	++	++	+++

These findings are in some respects contrary to recent reports. Changes in the electrocardiogram believed to be characteristic of vitamin B deficiency have been reported by several observers.<sup>2,12a,b</sup> But since these observations were not controlled, it is impossible to estimate the rôle of unknown factors. Jolliffe and his coworkers<sup>5</sup> recently reported electrocardiographic changes in human thiamin deficiency. It has been observed in animals<sup>8</sup> that deficiency of several factors of the B complex alters the manifestations of a single deficiency, so that the difference in results may represent a difference between the manifestations of thiamin deficiency alone compared to that of the entire B complex in the human.

2. GASTRO-INTESTINAL STUDIES. Mild anorexia was present after 1 week on the diet (Table 1) and ultimately became extreme. Other gastro-intestinal symptoms were heartburn, a constant sense of epigastric fullness, abdominal distention and constipation. Mild soreness of the tongue was an occasional complaint. Toward the end of deficiency nausea and vomiting were frequent, and during the last few days there was moderately severe generalized abdominal pain.

Appetite returned promptly following the administration of thiamin. Within 48 hours aversion to food was less extreme and by the end of 1 week a mild sensation of hunger was experienced. This return of appetite was not associated with any change in the other gastro-intestinal symptoms, except that the abdominal pain disappeared. Toward the end of the second week of thiamin therapy appetite again decreased and, in spite of the continued administration of thiamin and the addition of riboflavin, did not again return toward normal until yeast was given.

Roentgen examination of the gastro-intestinal tract (Table 2, Fig. 2) at the end of deficiency showed no abnormality except some increased calibre of the jejunal loops. After the subject had received thiamin for 18 days there was delayed gastric emptying and slight delay in small bowel motility. Increased calibre of the jejunal loops was still evident. Riboflavin did not significantly alter these findings. Following the administration of yeast, however, there was marked improvement in the small intestinal motility, the head of the barium column having reached the hepatic flexure 4 hours and 40 minutes after the ingestion of the barium, while under thiamin and riboflavin therapy a comparable film was not observed until 6 hours from the start of the examination. A slight delay in gastric emptying persisted. At no time were segmented and dilated loops of small bowel observed as described by Pendergrass and Comroe,<sup>9</sup> Mackie and Pound,<sup>7</sup> and Snell and Camp.<sup>11</sup>

3. NEUROLOGIC STUDIES. Three days after beginning the experimental diet diminution in electrical irritability of the peripheral nerves and some disturbance of sensation were observed (Table 3). A steady decrease in electrical irritability and exaggeration of the

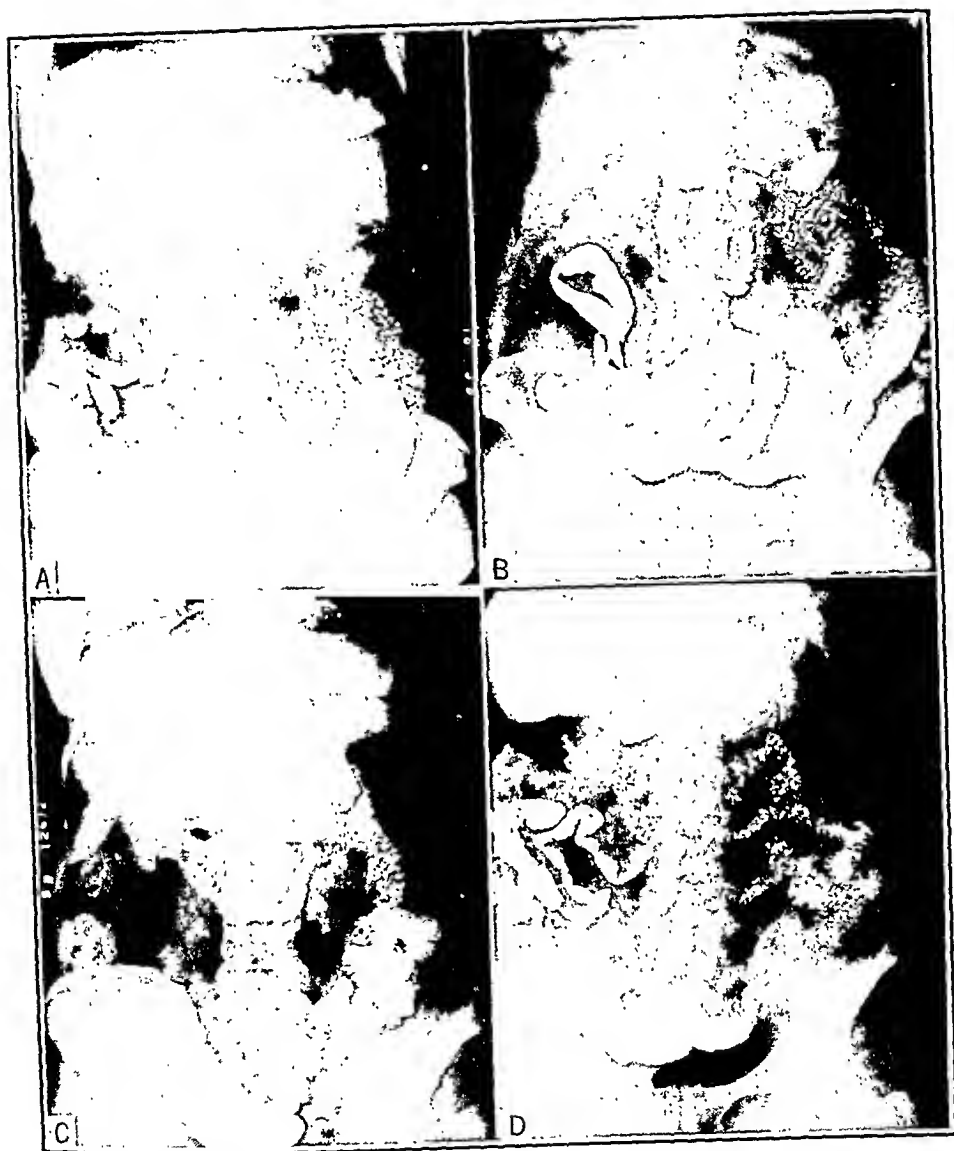


FIG. 2.—Roentgen examination of the gastro-intestinal tract 3 hours after administration of the barium meal: A, after 50 days on the deficient diet alone; B, 18 days of treatment with thiamin; C, 13 days of treatment with thiamin plus riboflavin; D, 16 days of treatment with brewer's yeast.



TABLE 2.—ROENTGEN APPEARANCE OF THE GASTRO-INTESTINAL TRACT.

	15 minutes.	1 hour.	2 hours.	3 hours.	4 hours.	5 hours.
Deficient diet	Normal gastric tone; occasional peristaltic rush in proximal jejunum	Motility gradual; pattern herring-bone in jejunum	Stomach empty; same as 1 hr. but barium now in ileum	Barium in ileum; snow flake pattern; ileum normal pattern, slightly widened caliber	Ileum nearly empty; head of meal at sigmoid	
Deficient diet + thiamin	Normal gastric tone; occasional peristaltic rush in proximal jejunum; fine reticular pattern in jejunum	Slow forward progression of barium in jejunum; herring-bone pattern	Delayed ileal motility	Gastric residue; delayed ileal motility	Gastric residue; delayed motility in small intestine; pattern normal	
Deficient diet + thiamin + ribo-flavin	Normal gastric tone; rapid motility in proximal ileum	Caliber normal; pattern herring-bone with gas in distal loops of jejunum	Barium reached the ileum; normal pattern and tone.	Gastric residue; delayed motility in ileum; normal pattern		Stomach empty; barium in cecum; pattern normal
Deficient diet + yeast	Normal gastric tone; rapid motility in proximal ileum	Small intestinal pattern normal	Normal ileal motility	Gastric residue; normal ileal motility; head of meal at cecum		Stomach and jejunum empty; head of meal at hepatic flexure

TABLE 3.—CHANGES IN NEUROLOGIC SIGNS AND ELECTRICAL IRRITABILITY OF THE PERIPHERAL NERVES.

Date.	Therapy. (time in days).	Neurologic signs.							Electrical irritability, $\mu C^*$ (normal 6-9).
		Sensitivity to		Tenderness.		Ataxia.	Corneal reflex.	Smell olfactics (normal 25).	
		Touch.	Pain.	Nerve.	Muscle.				
2/28	Deficient diet (3)	Bilateral hypesthesia, peroneal nerve from ankle to knee: 10-15 mg./mm. <sup>2</sup> (Normal 6)	Bilateral hypalgesia cut. femoral lat. nerve: 10 g. (Normal 2)	+	0	0	Normal	..	13.7
3/22	Deficient diet (25)	Hypesthesia right cheek	Hypalgesia right cheek	++	+	0	Hyperactive	25	10.0
4/7	Deficient diet (41)	Hypesthesia right cheek	Hypalgesia right cheek	++	+	++ arms	Hyperactive	20	13.4
4/25	Deficient diet (59)	Hypesthesia right cheek	Hypalgesia right cheek	++	+	+++ arms adiadokokinosis	Hyperactive	2	12.4
5/4	Thiamin† (4)	Normal	Normal	0	0	0	Normal	20	15.4
5/17	Thiamin (17)	Normal	Normal	0	0	0	Normal	..	9.6
5/29	Thiamin (29) Riboflavin (10)	Normal	Normal	0	0	0	Normal	..	8.8

\*  $\mu C$  = Microcoulombs.

† In the first 3 days the subject received 330 mg. of thiamin. Thereafter she received 60 mg. daily until 5/18, when the dose was reduced to 20 mg. daily for the remainder of the experiment.



clinical signs of peripheral nerve involvement occurred as deficiency progressed. Four days following the administration of thiamin all neurologic symptoms and signs had disappeared except electrical under-excitability. This continued for 17 days after the administration of thiamin, when the response again became normal.

4. MENTAL SYMPTOMS. Mental symptoms formed a striking part of the clinical picture. During the fifth week of deficiency the subject first complained of nervousness and irritability, which gradually increased in severity. Normally a very optimistic person, she became mentally depressed and frequently wept without cause. She lost all interest in her surroundings and disliked social contact. Sudden noises frequently caused distress although there was no alteration in auditory acuity.\* Loss of memory and inability to concentrate were prominent complaints. These symptoms regressed while thiamin was given but were not entirely relieved until yeast was added to the diet. In view of recent knowledge of the rôle of thiamin in the metabolism of brain cells,<sup>10</sup> it is conceivable that these mental changes were more than a simple reaction to a general physical inadequacy but represented true change in cerebral function.

TABLE 4.—BLOOD VALUES.

Period of observation.	R.B.C., millions.	Hgb., gm. per 100 cc.	Hematocrit, vol. %.	M.C.V.,* $\mu^3$ .	M.C.Hgb.,† gm. $\times 10^{-12}$ .
On admission . . . . .	4.24	13.45	37.8	89	31.7
Deficient diet (9th week) . . . .	3.85 (-9.0%)	13.3 (-0.8%)	37.8 (0.0%)	98.3 (+10.0%)	34.8 (+8.3%)
Deficient diet + thiamin (3d week) .	3.40 (-20.0%)	11.9 (-11.0%)	34.7 (-8.0%)	102 (+15.0%)	35.0 (+7.4%)
Deficient diet + thiamin + riboflavin (3d week)	3.42 (-20.0%)	12.9 (-3.7%)	37.0 (-2.0%)	109 (+22.0%)	37.8 (+18.7%)
Deficient diet + yeast (2d week) . .	3.25 (-24.0%)	12.9 (-3.7%)	38.0 (+0.5%)	120 (+35.0%)	39.7 (+24.0%)
General diet + yeast (4th week) . .	4.28 (+0.9%)	13.3 (-0.8%)	39.5 (+5.0%)	92 (+3.0%)	31.2 (-2.5%)

\* M.C.V. = Mean corpuscular volume.

† M.C.Hgb. = Mean corpuscular hemoglobin.

5. STUDIES OF THE BLOOD. Decrease in the number of red blood cells, increase in mean cell volume and hemoglobin, macrocytosis, polychromasia and poikilocytosis occurred (Table 4). These abnormalities were slight after 9 weeks on the deficient diet alone, but increased in spite of the administration of thiamin and riboflavin. Yeast added to the diet had no apparent effect for the final 2 weeks of the study, but it was continued on discharge from the hospital and 4 weeks later the blood had returned to normal. Dur-

\* We are indebted to Dr. O. V. Batson for audiographic studies.

ing this time the subject received a general diet, so that some other factor may have been responsible for the hematopoietic response. However, the fact that a similar type of anemia observed in pregnant women taking a vitamin B deficient diet<sup>3b</sup> responded to the administration of yeast suggests the presence in this substance of some active anti-anemic factor other than thiamin or riboflavin.

6. MISCELLANEOUS OBSERVATIONS. Certain general manifestations were evident early in the deficient period. Excessive fatigability was noticed and ultimately became extreme. The skin became pale, flabby and inelastic. The face assumed an expression of despair and the posture suggested extreme fatigue. Edema of the upper and lower extremities, present by the end of the first week, slowly increased. No explanation was found for the edema as the serum protein was normal and cardiovascular abnormalities were insufficient to account for it. Gradual loss of weight occurred in spite of the presence of edema.<sup>4</sup>

When thiamin was administered an immediate improvement was noticeable in strength, general appearance and skin texture. Skin color returned in spite of the fact that the anemia was increasing. Edema subsided and body weight increased. However, this improvement was temporary. After thiamin had been given for 10 days easy fatigability was again present and as described in the previous paper<sup>4</sup> increase in edema occurred and body weight declined. Riboflavin had no significant effect upon these findings, but when yeast was added to the diet the subject returned to normal.

7. MANIFESTATIONS OF DEFICIENCY IN 1933 AS COMPARED WITH 1938. Essentially identical experiments carried out in 1933 and 1938 provide a basis for comparison of the manifestations of induced deficiency. Certain similarities and differences seem worthy of mention. The outstanding clinical manifestations in each instance were changes in body weight, fluid balance and signs referable to the cardiovascular, gastro-intestinal, neurologic and hematopoietic systems. The time of onset of deficiency was comparable, approximately 5 weeks elapsing before signs of deficiency were definite. Anorexia was the first symptom to appear, and in both experiments symptoms preceded physical signs by from 2 to 3 weeks. The development of edema was the only exception.

In 1933, however, glossitis and neurologic abnormalities were prominent, while in 1938 though present, they were comparatively mild. Anemia was more pronounced in the present experiment as were mental and cardiovascular symptoms. While reasons for these differences were not clear, it is of considerable importance to realize that no single sign or symptom can be relied upon to provide a diagnosis of deficiency. A final observation deserves emphasis. Almost without exception the response to individual components of the B complex was both temporary and incomplete and a return to normal occurred only upon the administration of yeast.

**Summary.** 1. The clinical manifestations of vitamin B deficiency were studied in an otherwise healthy individual who consumed a constant daily amount of a standard diet adequate except for the B complex. These manifestations responded in part to thiamin, were influenced very little by the addition of riboflavin and were relieved by the administration of brewer's yeast.

2. Increase in pulse rate appeared during deficiency. It was associated with symptoms referable to the cardiovascular system. No change in the resting blood pressure, orthodiagram or electrocardiogram was observed. Cardiovascular abnormalities subsided during the administration of thiamin.

3. Gastro-intestinal symptoms developed during deficiency, and were associated with Roentgen evidence of delayed motility in the small intestine. Except for anorexia, which was promptly, though temporarily relieved by thiamin, gastro-intestinal symptoms were not relieved nor was there any improvement in the Roentgen evidence of delayed motility until after yeast was added to the diet.

4. Neurologic symptoms and physical signs were mild and were accompanied by decrease in electrical irritability. These abnormalities disappeared following the administration of thiamin.

5. Mental symptoms were prominent, responding somewhat to thiamin, but were not relieved entirely until yeast was added to the diet.

6. A mild macrocytic anemia developed during deficiency, which was uninfluenced by thiamin or riboflavin but was relieved after the subject had received a general diet and brewer's yeast for 4 weeks.

7. Edema of the upper and lower extremities appeared early in deficiency, was uninfluenced by the administration of thiamin or riboflavin. Gradual loss of body weight occurred in spite of the presence of edema. Edema disappeared and body weight returned to normal only after the administration of yeast.

8. The symptoms and physical signs in the present study were comparable with those observed in the same subject in 1933, although certain differences are described.

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## THE TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS WITH VITAMIN E (TOCOPHEROLS).\*

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IN a recent paper<sup>5</sup> I reported recovery in 2 cases of amyotrophic lateral sclerosis treated with synthetic vitamin E and discussed the theoretical reasons as well as the experimental knowledge (including references to literature) which led to the initiation of the treatment. Since then I had occasion to treat more than 30 cases. Of these, 15 were carefully observed and consistently treated by me. Five others were treated at the Montefiore Hospital† under my instruction but not under my personal care. These are nonetheless included in this report. The rest of the cases were not adequately studied. Some were seen but once, others were not consistently or sufficiently followed or studied, in still others the question of diagnosis was obviously in doubt.

The results of treatment‡ have confirmed the tentative opinion expressed in the preliminary report. A number of facts have come to light, which require further experimental investigation. Experimental deprivation of vitamin E is now being carried out in monkeys. Creatine-creatinine determinations, liver function studies, investigation of gastro-intestinal enzymes and other vitamin deficiency studies have been carried out in many of the patients. These too will be reported upon as soon as enough facts are gathered. Herein a number of general observations will be discussed briefly to outline the scope of the investigations; thumb-nail case reports to establish the diagnosis in each instance will be given, and a few general conclusions justified by the facts thus far will be drawn. The importance of these studies to other so-called degenerative disease of the nervous system and to their possible relation to problems in internal medicine (cirrhosis of the liver, nephrosis) will also be alluded to. Finally, the clinical observations, particularly as to age, sex and duration of the disease, point to the need for a newer evaluation of the whole clinical syndrome.

**Case Reports.** CASE 1.§—A. L., male, age 52, began to complain of weakness and tiredness of the left hand in July, 1939. He gradually lost

\* Read at the Meeting of the American Neurological Association, June 6, 1940, Rye, N. Y.

† I am grateful to Dr. Victor Rosen, the Resident in Neurology, who kindly supervised studies and treatment.

‡ The Hoffmann-LaRoche Company kindly furnished me the tocopherol acetate tablets for the treatment of all patients under my care and Merck & Co. supplied me with the tocopherol in oil for intramuscular injection. I wish to make herewith grateful recognition and to thank Drs. R. D. Shaner and D. F. Robertson respectively for their most generous help and coöperation.

§ Cases 1 and 2 were previously reported.

power in the hand. Early in October his legs began to tire. When first seen on October 18, 1939, he showed increased deep reflexes on the left side, diminished left abdominals and absent left plantar reflex, weakness of the hand with wrist drop, atrophy of the small muscles of the hand, weakness of the forearm, shoulder girdle, and occasional fibrillations. He was admitted to the Mount Sinai Hospital and treatment was begun on November 13, 1939. Return of power began to appear in a few days, and within a few weeks the wrist drop cleared up and he could use his fingers in skilled movements. On 2 occasions treatment was interrupted for several days and weakness began to return. He has been kept on Ephynal to date and is doing well.

CASE 2.—C. B., female, age 36, was admitted to the hospital in August, 1939. Weakness of the arms and legs began in August, 1938. After several months she began to develop difficulty in speaking and swallowing. On examination she showed marked atrophy of the muscles of all the extremities, and particularly of the hand muscles and the tongue; universal fibrillations most marked in the tongue; all the deep reflexes were hyperactive and there was bilateral clonus. The patient was practically bedridden and unable to feed herself. Treatment was begun in October, 1939. The fibrillations disappeared, the tongue began to fill out and to lose its fibrillations and within 2 months she was able to walk. On re-admission for purposes of check-up in March, 1940, the patient showed no fibrillations, and was able to walk and feed herself. She is now able to do some housework. She swallows and speaks well. Her diet had been deficient in vitamins in that she ate none of the vegetables containing it.

CASE 3.—L. O., male, age 24, was admitted to the Mount Sinai Hospital on January 8, 1940. The disease began in October, 1938, with weakness of the hands and feet. The weakness gradually increased so that he had difficulty in walking and in using his hands. On examination the patient showed steppage gait, inability to walk on his heels, hyperactive deep reflexes, absent abdominals, bilateral Babinski signs, marked atrophy of the deltoids, trapezii and small muscles of the hands with moderate atrophy of the muscles of the thighs, calves and feet. Fibrillations were present in the masseters, tongue, neck, shoulder and arm muscles and the thighs and calves. Treatment was kept up in the hospital for 2 months. The patient stated that he felt better and stronger; actually there was no objective evidence of improvement except possibly for diminution of fibrillations. The condition was regarded as arrested but not improved. While in the hospital he developed pharyngitis during which he showed marked weakness.

CASE 4.—L. G., male, age 36, began to have weakness of the legs in March, 1939. For 1 year before the onset of the illness he lived on a restricted diet poor in vitamin E because of gall bladder disease. Weakness of the hands soon followed and generalized fibrillations appeared in June, 1939. When first seen on January 27, 1940, he had marked spasticity in both lower extremities, universally increased deep reflexes with bilateral Babinski reflexes and clonus, generalized fibrillations, weakness of the shoulder and arm muscles and almost complete paralysis of the hand muscles, atrophy of the supra- and infraspinati, deltoids, pectorals and all the small muscles of the hands. Treatment was begun in February and has continued to date. The fibrillations have practically disappeared, walking is somewhat improved and some power has returned in both thumbs. The case may be regarded as definitely arrested and somewhat improved.

CASE 5.—R. E., female, age 39, began to have weakness of the hands and forearms in July, 1938. Gradually the legs became weak. It is of interest that she ate few vegetables, little fruit, not much bread, and no cereals or bananas. She was seen in the office on February 7, 1940, when she showed a spastic gait, occasional fibrillations in the triceps muscles and in the right

side of the tongue, markedly increased deep reflexes with clonus and questionable Babinski sign, weakness of all muscles of the hands, biceps, triceps and deltoids on both sides and marked atrophy of all the muscles of the hands. She was admitted to the Mount Sinai Hospital on February 26 and remained for a month. She began to improve rapidly and left the hospital able to walk fairly well and much stronger in the hands. Repeated follow-up examinations since discharge from the hospital showed sustained improvement.

CASE 6.—A. R., female, age 49, was admitted to the hospital in a moribund condition on March 25, 1940. The history obtained, because the patient could not speak, was unreliable. It seems that the condition began late in 1937 with weakness of the upper extremities. On admission she had cardiac failure. She drooled saliva, was unable to articulate and could not swallow. Within 24 hours the cardiac decompensation was relieved by treatment. It was then observed that she had generalized muscular atrophy and weakness, practically complete paralysis of the extremities, bulbar and pseudobulbar involvement, with aphonia, dysphagia and explosive laughter and crying, generalized hyperreflexia, except for the left knee jerk, few general fibrillations but marked ones in the tongue. She had to be tube fed and vitamin therapy administered through the tube. Within a few days she began to show improvement. This continued progressively until she could chew and swallow solid foods. The drooling disappeared, there was no more dysphagia, nor explosive laughing or crying. She could now hold up her head and sit up in bed. Altogether this represented a remarkable and spectacular reversal of bulbar signs and symptoms in a person who was practically dying on admission. The bulbar recovery has been maintained to date.

CASE 7.—R. T., male, age 58, was admitted to the Mount Sinai Hospital on March 4, 1940, with the complaints of difficulty in swallowing, inability to speak, and excessive salivation. The condition began very rapidly in April, 1939. The syndrome was essentially bulbar in character. There was generalized hyperreflexia with patellar and ankle clonus. There was slight atrophy of the muscles of the left leg. Fibrillations were very marked and generalized, including the face and the tongue. The tongue could only be protruded as far as the teeth; it showed some atrophy. On treatment the salivation diminished greatly, the swallowing became less difficult. The tongue could be protruded just beyond the teeth. After a stay of 7 weeks, the patient was discharged slightly improved. Only the bulbar involvement seemed to be arrested during the stay in the hospital.

CASE 8.—N. W., female, age 40, began to complain of weakness of the hands, 18 months before admission to the hospital on March 22, 1940. In March, 1939, she began to have difficulty in speaking, swallowing and breathing. On admission her speech was unintelligible, she could not hold her head up unsupported and dragged her right leg in walking. Fibrillations were generalized but especially pronounced in the arms, neck and tongue. The left knee jerk was hyperactive, all the other deep reflexes were sluggish. There was a suggestive left Babinski sign. There was bilateral facial weakness, marked weakness of the sternocleidomastoids and trapezii, and the tongue, which was atrophic, could not be protruded beyond the lower lip. There was atrophy of the small muscles of both hands. The patient was unable to turn in bed or sit up without assistance. As soon as the treatment was begun she began to show improvement, and by the time of her discharge on April 13, 1940, her speech had become intelligible, she could hold her head without support and was able to feed herself and walk about the ward. For a few days when she had a mild upper respiratory infection there was a temporary relapse, with rapid recovery when the infection cleared up.

TABLE 1.—RESULTS OF TREATMENT.

No.	Case.	Age.	Sex.	Duration, mos.	Ther- apy, wks.	Atro- phy.	Fibril- lations.	Py- r. tract signs.	Bulbar signs.	Defect. vit. E diet.	Other.	Results.
1	A. L.	52	M	3	30	+	+	+	0			Recovered
2	C. B.	36	F	15	26	++++	++++	++++	+++	?		Improved Esp. bulbar
3	L. O.	24	M	15	17	++	++	++	+			Arrested
4	L. G.	36	M	11	13	++++	++++	++++	0	1 yr.	Gall bladder diet	Improved
5	R. E.	39	F	20	13	++	++	++	+			Marked improvement
6	A. R.	49	F	30	6	++++	++++	++++	++++		Heart failure	Marked improvement
7	R. T.	58	M	11	6	+	++	++	+++			Arrested Sl. improved
8	N. W.	40	F	18	6	+++	+++	+++	+++			Marked improvement
9	R. A.	16	F	5	6	++	++	+++	0			Marked improvement
10	P. W.	49	M	11	3	++++	++++	++++	++++	?	Carcinoma pancreas	Improved Died—Pn. Cancer
11	E. H.	45	F	6	5	++	+	++	0	3 yrs.	Bacillary dysentery	Recovered
12	S. Y.	46	M	12	13	+++	+++	+++	++		Pleocytosis Enceph.?	Worse
13	E. H.	37	M	13	14	+++	+++	+++	++	3+ yrs.	Diet deficient	Improved Relapse
14	H. H.	56	F	24	6	++	0	++	0		Hepato- biliary dis.	Arrested Sl. improved
15	W. Z.	21	M	3	4	+	+	++	0			Improved
16	L. G.	60	F	24	8	+++	+++	+++	+++			No change Arrested?
17	R. M.	62	F	17	14	+++	++	+++	0			Worse—bulbar
18	A. K.	49	F	20	14	+++	++	+	++			Sl. worse
19	D. S.	54	M	42	14	+++	++	0	+			Improved
20	J. B.	50	M	8	13	+++	+++	++	++++			Died—Pn.

CASE 9.—R. A., female, age 16, was admitted on March 25, 1940, with the history that in October, 1939, she first noticed weakness of the fingers in typing. Two months later she was unable to approximate the thumb to the tips of the other fingers. At the same time fibrillations were noted in the left arm and right thigh. In February, 1940, weakness of the legs set in, so that she had difficulty in walking, kneeling, and climbing stairs. On occasion she would fall. The weakness of the hands became very

marked. On examination there was atrophy of the small muscles of the hands with early claw-like deformity, poor adduction, flexion, and extension of all the fingers, marked motor weakness in the arms and legs, generalized hyperreflexia with ankle clonus and Babinski signs, absent abdominals, and fibrillations in the deltoids, biceps, hand muscles and thighs. Put on vitamin E therapy, she promptly began to show improvement. Soon she could lift a pitcher of milk, she began to walk without fatigue, the fibrillations decreased markedly, and on discharge, May 2, 1940, she was markedly improved. She has continued to do well. This is the first instance that we know about of amyotrophic lateral sclerosis in a person so young.

CASE 10.—P. W., male, age 59, was admitted on April 23, 1940, with the history that in May of the previous year he began to have weakness of the right hand rapidly involving the right leg and the left arm and leg. His gait became stiff and the fingers of the hand contracted. Very soon he found difficulty in swallowing and speaking and felt twitching of the tongue. On admission he was aphonic, could not swallow and salivated profusely. On examination he showed bilateral hyperreflexia with ankle clonus, fibrillations all over the body and limbs and particularly the tongue which he was unable to protrude. He was only able to raise his right arm and leg a few inches from the bed. As soon as vitamin E was given his swallowing began to improve and his respiratory distress lessened. He seemed to be improving when he developed an acute streptococcus pharyngitis. Swallowing became once more difficult, he developed pneumonia (not aspiration) and died 24 days after treatment was begun. On necropsy carcinoma of the pancreas was found.

CASE 11.—E. H., female, age 45, was first seen on April 2, 1940. She had been suffering from bacillary dysentery for 3 years before the onset of the present illness, which was in September or October, 1939. She ate very little and practically none of the articles of food containing vitamin E. There was also a history of migraine dating back many years. The present illness began with weakness of the left toes, falling on walking downstairs and increasing weakness, which now involved the whole foot and leg. Fibrillations of the thighs were first noticed in February, 1940. On examination she showed left foot drop and a total loss of power in all the muscles of the foot. All the deep reflexes were markedly increased with bilateral clonus, more marked in the left foot, and a suggestive Babinski sign. The left foot and leg showed atrophy. Treatment with vitamin E brought about prompt improvement. Within 2 weeks she discarded a brace which she had been wearing. By the end of the month she could walk on toes and heel, and when last seen on May 7 had recovered most of the power in the foot. Once during the course of observation when treatment was interrupted for a few days, the weakness returned only to disappear with resumption of treatment. Subsequent reports tell of reappearance of fibrillations.

CASE 12.—S. Y., male, age 46, was first seen privately on February 1, 1940. His illness began in February, 1939, with weakness of the right hand, then of both legs, and in June of the same year of the left hand. About a year later his voice began to give out and he complained of choking and difficulty in swallowing. On examination he showed marked atrophy of the muscles of both hands, arms, and shoulder girdles, weakness of both legs, and generalized fibrillations, including the tongue. There was marked hyperreflexia, including the jaw jerks, and extreme loss of power in both upper extremities. The picture was classic of amyotrophic lateral sclerosis, except that the question of chronic encephalitis was raised at a hospital where lumbar puncture was performed and 19 cells were found in the spinal fluid. He was placed at first on 15 mg. of Ephynal daily, and 2 weeks later a diet rich in vitamin E was given. At the end of the third week his swallowing had improved somewhat. The whole wheat germ oil and bile salts



were then added. He continued to improve until the end of April when the condition began to grow worse. Swallowing became more difficult and fibrillations of the tongue became more pronounced. Despite continued treatment the patient has continued to lose ground. He refused to enter the hospital nor would he rest at home. He is a poor junk dealer who was compelled to do what little work he could in order to earn a living.

CASE 13.—E. H., male, age 37, began to have twitching of the right arm, forearm and hand in January, 1939. Two months later the left arm was similarly involved. At this time atrophy of the hand appeared. In July of the same year the legs began to get stiff. On examination the patient showed very spastic gait, marked weakness of both lower extremities, almost complete loss of power in the hands, and weakness of the forearm and shoulder muscles. There was complete atrophy of all the small muscles of the hands and marked atrophy of the arms, forearms, pectorals and leg muscles. There was marked hypertonia in the lower extremities. Fibrillations were numerous in the shoulder, chest, and arm muscles, in the abdomen and thighs and slightly in the tongue. All the deep reflexes were markedly increased; there was bilateral ankle clonus and Babinski sign. Treatment was begun at first with alpha-tocopherol acetate, then followed by the other additions. His gait became more steady, he no longer fell in walking, and the fibrillations seemed to lessen. The condition remained stationary for about 2 months, then began to progress so that the patient is now worse. Of interest in this case is the fact that this patient thrived for some time up to his first visit to the office on a diet almost completely devoid of vitamin E.

CASE 14.—H. H., female, age 56, was first seen on March 30, 1940, when she complained of weakness of the hands and legs. The condition began gradually in 1938, possibly in 1937, and has become progressively worse. In March, 1938, both hands were very weak and in October, 1939, the legs became weak. Physical examination showed generalized weakness with bilateral foot drop, more marked on the right side. There were no fibrillations, the deep reflexes were present and equal but not hyperactive. There was weakness of all the muscles of the hands, of the forearm and arm muscles, of the shoulder girdles and of the dorsiflexors of the feet. There was atrophy of the interossei, thenar and hypothenar eminences, of the forearms, of the left supraspinatus and the peronei of both legs. The presence of hypotonia and the absence of a Babinski sign militated somewhat against the diagnosis of amyotrophic lateral sclerosis, but the presence of reflexes, though not increased, and the presence of atrophy spoke in favor of the diagnosis. The patient was put on vitamin E treatment but did not improve; in fact, she seemed to grow weaker. She was admitted to the hospital for further study. There it was found that she had one gall stone and she showed impaired liver function. Treatment restored her appetite and she seemed to improve.

CASE 15.—W. Z., male, age 21, began to complain of weakness of the right hand in January, 1940. The father of the patient insisted that he noticed thinning of the right hand several months before that date. All the deep reflexes were hyperactive. A few fibrillations were noted in the anterior part of the right forearm. There was weakness of the extensor, adductor and opponens of the right thumb, and weakness of the extensors of the wrist and of the first phalanges of the right hand. There was atrophy of the first interosseous space, of the thenar and hypothenar eminences, of the dorsum of the hand and slightly of the forearm and biceps, all on the right side. Intensive treatment was begun on April 26, 1940. On re-examination on June 4, he showed considerable return of power in the hand. The patient no longer tires when writing; he just passed several 4-hour written examinations without fatiguing.

CASE 16.—L. G., female, age 60, began to complain in March, 1938, of generalized weakness. Soon difficulty in swallowing appeared and in the past year progressive dysarthria. The outstanding signs were atrophy and fibrillations of the intrinsic muscles of the hand, general hyperreflexia, including the jaw jerk, bilateral paresis of the palate and the muscles of mastication, and atrophy and fibrillations of the tongue. Altogether this was a very advanced case. Treatment was begun on March 15, 1940. No subjective or objective improvement occurred.

CASE 17.—R. M., female, age 62, began to complain September, 1938, of weakness of the hands and 2 months later of weakness of the legs. On neurologic examination she showed spastic gait with hyperreflexia and ankle clonus and atrophies and fibrillations in the hands, forearms, shoulders and thighs; also aphonia. Despite treatment, which was begun on February 5, 1940, progressive bulbar involvement with dysarthria, dysphagia and atrophy and fibrillations of the tongue appeared.

CASE 18.—A. K., female, age 49, began with dysarthria, hoarseness and pain in the throat followed by generalized weakness in April, 1938. The essential neurologic findings were spastic gait on the right, hyperactive jaw jerk, all other deep reflexes only moderately active, atrophy and fibrillations of the tongue, bilateral atrophy of the deltoids, bilateral motor fifth paresis, deviation of the uvula to the right, and dysarthric bulbar speech. Treatment was begun on February 5, 1940. There has been no improvement to date; indeed, there may have been slight progressive involvement.

CASE 19.—D. S., male, age 54, began to complain August, 1936, following spinal anesthesia for herniorrhaphy, of stiffness and pains in the back of the neck and gradual weakness of the muscles of the shoulders. Following this there was bulbar involvement. On neurologic examination he showed marked atrophy and occasional fibrillations in the muscles of the shoulder girdles and upper arms and hemiatrophy and fibrillations on the right side of the tongue. There were no pyramidal tract signs. Treatment was begun on February 7, 1940. He began to show increasing strength in the muscles of the shoulder so that he could raise the arms and touch the top of his head, something he could not do before treatment. The fibrillations of the tongue disappeared and there was possibly some filling out of the muscles of the right upper arm and shoulder.

CASE 20.—J. B., female, age 50, began to show weakness of the upper extremities in June, 1939, rapidly followed by difficulty in swallowing and progressive involvement of speech. Neurologic examination showed spastic gait, atrophy of the intrinsic muscles of the hands, generalized fibrillations, bilateral involvement of the motor fifth nerve, palatal paresis, bilateral atrophy and fibrillations of the tongue, weakness of the sternocleidomastoids and trapezii, and marked dysarthria. Treatment was begun on February 7, 1940. Despite this she progressed rapidly downward and died on May 13, 1940. (Necropsy to be reported.)

**Treatment.** The treatment thus far consisted of the administration of Ephynal or alpha-tocopherol acetate by mouth, at first 30 and later 50 mg. daily.\* In about one-half of the cases 50 mg. of tocopherol in oil were injected daily intramuscularly. All patients received the following articles of food containing vitamin E, the first three being the richest: lettuce, kale, whole wheat bread, coarse cereals, butter, bananas, fresh corn, fresh peas and beans,

\* Prolonged experience indicates that this dose is too small in some cases and that 100 to 200 mg. are necessary.

yolks of eggs, and fat beef. Because vitamin E is fat soluble and because it has been shown that the fat-soluble vitamin K is better absorbed if bile salts are added, 2 5-gr. pills of bile salts were given daily. Where the bile causes diarrhea it is well to give Bilron which contains iron. Every patient received daily 2 teaspoonfuls of whole wheat germ oil. In the past month the extracted rather than the pressed oil was used in the belief that the former is less apt to contain unsaturated fatty acids which may cause deterioration of the vitamin E. Whether the one is more effective than the other cannot be determined from the present studies. Based on the assumption that vitamin B<sub>1</sub> or the filtrate factor, can cause atrophy, the whole B complex has also been given. Whether it is necessary or not is still a question.

TABLE 2.—RELATION BETWEEN DURATION OF DISEASE AND THERAPEUTIC RESULTS.

Duration, mos.	Died.	Worse.	Arrested.	Im- proved.	Mark- edly im- proved.	Recov- ered.	Cases.
3 . . . . .	..	..	..	..	..	1	1
4-6 . . . . .	..	..	..	1	1	1	3
6-8 . . . . .	1	..	..	..	..	..	1
9-11 . . . . .	1	..	..	2	..	..	3
12-17 . . . . .	..	3	1	1	..	..	5
18-24 . . . . .	..	1	2	..	2	..	5
Over 24 . . . . .	..	..	..	1	1	..	2
Cases . . . . .	2	4	3	5	4	2	20

TABLE 3.—RELATION BETWEEN SEX AND RESULTS OF THERAPY.

	Died.	Worse.	Arrested.	Im- proved.	Mark- edly im- proved.	Recov- ered.	Cases.
Males less than 6 months . . . . .	..	..	..	1	..	1	2
Males more than 6 months . . . . .	2	2	1	3	..	..	8
Females premenopause . . . . .	..	..	..	1	4	1	6
Females postmenopause . . . . .	..	2	2	..	..	..	4
Cases . . . . .	2	4	3	5	4	2	20

There is some evidence to show that lettuce contains a factor lacking in the germ oil, and, conversely, that there is something in wheat germ oil which is not present in the lettuce; so that the administration of either alone will not cure sterility or abortion in animals, whereas the administration of both will. This is the reason why both the synthetic products and the wheat germ oil as well as the foods rich in vitamin E were given. It is a fact that in 2 cases the administration of alpha-tocopherol acetate alone brought about improvement. In order to insure, if possible, more rapid and pronounced improvement it was thought advisable to saturate the patients and give both the synthetic and natural vitamin E. Now that the fact has been established that improvement can be brought about, one group of patients will be given only the synthetic, the other only the natural vitamin E by mouth. Whether or not the intramuscular injection is superior to oral administration

also cannot as yet be stated. Two patients seemed to show improvement only after the injections were started; in the rest this did not hold. Again, for scientific accuracy, it will be necessary to divide cases into groups for purposes of oral and parenteral administration respectively.

In 2 instances it could be clearly shown that stopping the administration of vitamin E brought about a relapse, which promptly was reversed the moment vitamin E was readministered. This may be of crucial significance. Only two such experiments were purposely undertaken. More such trials will have to be made in the future.

The dosage is not yet established. It seemed at first that 50 mg. of tocopherol daily were adequate. From the work of MacKenzie and McCollum<sup>3</sup> it appears that rabbits need from 0.7 to 1 mg. of tocopherol per kilo of body weight to cure muscle dystrophy. Applying the same figures to humans weighing, say, 60 kilos, it would seem that 50 mg. daily are sufficient. Very probably this is a minimum dose, although it is amply supplemented with the vitamin E in the diet.

The question arises whether patients will have to be treated permanently with synthetic or natural vitamin E. From *a priori* evidence and from observation of patients it would seem that they will, unless of course the cause of failure to absorb is discovered and removed. Why, in view of the fact that natural vitamin E is so prevalent, there is failure of absorption and why if there is failure it occurs only in certain persons and not in others is a question which can be raised but not answered at this time.

One thing may be stated with assurance, namely, that those patients who promise recovery show improvement fairly rapidly. This applies to the disease as a whole as well as to the most recently developed sign which is most likely to recede. The fibrillations are apt to disappear first, thus indicating a recession in the activity of the disease process. These observations are in accord with what is already known of the action of other vitamins. In the first place, it is probably true that the absence of vitamins acts in a specific way upon special tissues. Secondly, the administration of vitamins when effective acts specifically in a curative way. If this is true, it may be pointed out parenthetically that the indiscriminate administration of some or all of the vitamins on so-called general principles is not justified. Thirdly, although partial privation of vitamins over a long period of time may give subclinical manifestations, pronounced clinical syndromes are apt to appear rather rapidly. Fourthly, being specific, the administration of vitamins is apt to bring about fairly rapid recovery even in chronic conditions, always provided that dosage is adequate and absorption effective. It would seem logical to expect that the earlier the case and the more reversible the destruction of nerve tissue the more effective the treatment. In general this is true, but it does not always hold.

Besides there is reason to believe the term reversible may have to be redefined; what appears irreversible now may be shown to be reversible in the future. Nonetheless early and intensive treatment, and this presupposes early diagnosis, is imperative if results are to be obtained.

**Analysis of Cases.** Study of the three tables will reveal that 11 out of the 20 cases showed varying degrees of improvement. Two patients seem to have recovered, 4 showed marked degrees of improvement and 5 moderate degrees. A. R. (Case 6) was practically moribund, had very advanced bulbar signs, and was expected to die within a few days. The administration of vitamin E by means of stomach tube and intramuscular injection restored completely the functions of chewing and swallowing, and within a short period of a few weeks she could sit up in bed, hold up her head and feed herself. From a bedridden state C. B. (Case 2) now goes about her house, feeds herself and is moderately active. R. A. (Case 9), whose left foot was totally paralyzed, has almost completely recovered its use. Three patients may be said to have the disease arrested. Two patients with very advanced disease and bulbar signs died. One of these began to show improvement in his bulbar signs but died of pneumonia. At necropsy cancer of the pancreas was found, a fact which may prove to be of importance. The other patient died of bulbar involvement. Two patients have definitely grown worse and of the 2 others 1 is worse after initial improvement and the other is only very slightly worse.\*

The sex factor is of interest. Except for the 1 male who seems to have recovered, whose illness had been of but 3 months' duration, the 6 patients showing marked improvement were all females, and all were of the premenopause age. One of these women improved remarkably, 1 other improved greatly, 2 recovered from advanced bulbar involvement, 1 other showed marked and 1 moderate improvement. Some improvement occurred in 4 males, and in 1 female in the premenopause age. Two females of the postmenopause age showed what appears to be arrest of the process; only 1 male had the disease arrested. Two males whose illness was of long duration and 2 females of the postmenopause age have grown worse; of the 2 that died both were males. While these facts seem to be important, observation of more cases and over a longer period of time than the 8 months since this investigation was begun will be necessary before drawing final conclusions. It should be stated that the incidence of amyotrophic lateral sclerosis in my whole series is greater in males than in females. Another point worth noting is that neither libido nor potency was affected in the males. Whether men with the disease become sterile is another factor. This point will be investigated. It is relevant to mention in this connection

\* Since this paper was submitted for publication 1 patient, L. O., has grown worse and another, R. T., with very advanced disease, died.

that experimental evidence derived from work with animals confirms in some measure the clinical observations. Sterility in female animals, tendency to abortion, or marked reduction in the number of the litters, if brought about by the privation of vitamin E, can generally be reversed by the administration of vitamin E. In males, once sterility is brought about, and particularly if the testes are atrophied, the process cannot be reversed.

**Clinical Considerations.** Amyotrophic lateral sclerosis has always been regarded as such a sharply defined entity that questions of diagnosis rarely came up. Atrophies, fibrillations and increased deep reflexes are taken to be absolutely pathognomonic. The disease syndrome has been regarded invariably as progressive and ultimately fatal from bulbar palsy within 2 or 3 years. It has always been stated that it occurs past middle life. But the clinical study of the 20 cases herein reported and of 10 additional ones (report of which will appear separately) points to the need of revising some well-established concepts. To begin with, there are at least three and possibly four varieties of amyotrophic lateral sclerosis syndromes. One occurs on the basis of inflammation, generally chronic encephalitis, as Wimmer first showed. Here we are obviously not dealing with a vitamin deficiency. Another small group may be the result of vascular disease, possibly luetic; and in older patients, certain bulbar syndromes, cannot be distinguished from the more usual disease. These, too, are presumably not the result of avitaminosis. In none of these may one expect recovery with vitamin E therapy, but some of those patients may live for years and years. Conversely, the absence of recovery may raise the question whether the syndrome under treatment truly belongs to the third and largest group, namely the so-called degenerative type. It is the last alone which appears to be the result of vitamin E privation and in which favorable response to vitamin E therapy may be expected.

As to age grouping, we have one girl of 16. As far as is known it is the youngest case on record. Two cases occurred in men of 21 and 24 respectively, and 4 others in patients below 40. Only 7 were 50 and over. Another point is the early occurrence of bulbar signs in a large proportion of cases. Usually bulbar symptoms are the last to appear. In some instances involvement of the arms, legs and body was so minimal and the increase of deep reflexes so moderate (sometimes they were absent) that the diagnosis was justly in doubt. This applies to some of the last 5 cases included in this report. Another point worth noting was the excessive salivation in some patients with bulbar involvement. Generally this is attributed to paralysis of the tongue and impairment of swallowing, but in some cases it was so excessive as to raise the question whether the salivatory nucleus in the medulla was also affected. Finally, it is not sufficiently stressed that pseudobulbar symptoms may dominate the bulbar signs and that the loss of voice

and speech may be the result of involvement of the pyramidal fibers as they go from the cortex to the bulbar nuclei rather than of the motor nuclei themselves. That this is true may be inferred in part from the results of treatment. In several patients who responded to the vitamin E the bulbar signs, the more recent ones, cleared up and the patients chewed and swallowed well, no longer salivated and could hold up their heads; whereas the pseudobulbar symptoms, probably the older, responded less well or not at all. This was especially true of Cases 6, 7 and 8. Another point worth recording is the invariable interruption of recovery, sometimes to the point of relapse, by an acute infection, even a mild respiratory one, followed by renewed improvement after the infection was over. This is an observation which seems to hold true in other non-infectious diseases of the nervous system.

**Other Degenerative Diseases.** If the facts herein presented are correct, two deductions, each of major importance, may be made. First, that vitamin E deficiency, probably of the  $\alpha$ -tocopherol factor, is one cause of amyotrophic lateral sclerosis and that the administration of vitamin E may be a specific treatment. The importance of this observation, if corroborated by further studies, lies in this, that a so-called degenerative disease hitherto accepted as invariably progressive and fatal, for which there was no treatment and the cause of which was unknown, can be successfully treated in some cases, improved in some others and possibly arrested in still others. Second, these studies open a new page in the understanding and possibly the treatment of other diseases of the nervous system which for want of better knowledge we called degenerative. As a corollary, one may point to the relationship of these studies to the understanding of certain problems in internal medicine. Both hepatic cirrhosis and nephrosis, like degenerative diseases of the nervous system, are end products of obscure pathologic processes which have gone before, and most of the present studies are directed to the elucidation of functions which have been perverted by largely unknown antecedent factors.

Now, the word degeneration is an anatomico-pathologic term usually describing a process which has already spent itself. It tells nothing about causes or pathogenesis. What is meant by the term sclerosis of the nervous system is that myelin sheaths, nerve fibers and nerve cells have disintegrated and glial tissue, that is, a scar, took their place. With other tissues and organs vascular changes and connective tissue scars parallel the glial proliferation. It was dissatisfaction with the label degeneration in the central nervous system, just as it was dissatisfaction with the vague terms toxic and infectious in the case of peripheral nerves, that led to these studies. It has long been suspected that the pathologic processes in so-called degenerative diseases resemble some of the pathologic processes in the nervous system known to be due to vitamin priva-

tion. The recognition that the absence of one vitamin may be the specific cause of one "degenerative" disease, naturally leads to the assumption that other vitamins may play a rôle in the causation of other "degenerative" diseases of the nervous system. This appears to be true, and the evidence at hand justifies a certain amount of theoretical speculation.

A few observations, by way of caution are, however, worth making. First, it does not follow that, because certain syndromes bear some resemblance to each other, they are necessarily related or caused by the same factor. Sclerosis like degeneration, is a final descriptive term. Second, similar clinical end results or disease entities may be the result of different causes. Thus multiple sclerosis is not a disease but a congerie of syndromes of varying etiology though the syndromes look clinically very much alike. There are at least three different kinds of multiple sclerosis—possibly more—due to inflammation, allergy and possibly vitamin deficiency. Third, it is well to bear in mind that the nervous system has specific selectivity for drugs, toxins and infections, and different structures react specifically to vitamin, oxygen, sugar or other deficiencies. Certain parts are more sensitive than others and varying structures differ biochemically in their constitution and therefore in their reaction. Add to this the fact already alluded to, that vitamins act specifically, and it becomes clear why analogies alone are not sufficient and why all the degenerative diseases cannot be indiscriminately treated by one vitamin because this vitamin happens to be effective in one of them. From what is known already it may be predicted that certain "degenerative" disease will be found to be the result of the privation of specific vitamins though other factors may play additional rôles. Recent observations that absence of B<sub>6</sub> may be a factor in "degenerative" paralysis agitans, not in the arteriosclerotic or inflammatory types, illustrate the point.

The dystrophies illustrate another syndrome which seems to be the result of vitamin privation. It will be recalled that Bicknell's<sup>2</sup> paper dealt largely with the dystrophies and only incidentally with amyotrophic lateral sclerosis. He reported recoveries in several patients treated with wheat germ powder. He did not use the synthetic vitamin E or the tocopherols. More recently Stone,<sup>4</sup> reported on the treatment of muscular dystrophies and "allied" conditions with vitamin E. As has been pointed out, "allied" is a vague term and should not be used. But Antopol and Schotland<sup>1</sup> reported good results after treatment of dystrophies with vitamin B<sub>6</sub>. It is also worth noting that the dystrophies belong to the so-called heredo-generative diseases. That is, there seems to be a genetic factor in addition to vitamin deficiency. My own experience is limited to a few patients with dystrophies, all of whom have been treated both with the synthetic as well as the natural vitamin E. In none have I seen thus far rapid or really pronounced



recoveries. The patients say they feel better. One believes that he is stronger and one rises normally from a supine position instead of climbing upon himself as he did previously. Much further study is necessary to justify positive conclusions, though the evidence so far adduced is worthy of the utmost consideration.

**Conclusions.** 1. Twenty cases of amyotrophic lateral sclerosis treated with vitamin E have been studied and the results reported.

2. Privation of vitamin E plays a specific rôle in the causation of some types of amyotrophic lateral sclerosis, but other factors also operate in an as yet unknown manner.

3. Synthetic vitamin E (*i. e.*, alpha-tocopherol) and natural vitamin E act specifically in some cases and bring about varying degrees of improvement, perhaps in inverse ratio to the age and duration of the disease process. Some cases, for reasons not yet clear, fail to respond despite intensive treatment.

4. Dietary deficiency, gastro-intestinal and hepatic disease, possibly the absence of other vitamins, may play additional causative rôles. Some of the evidence points to interference with the absorption of the vitamin E.

5. There is evidence pointing to the probability of vitamin deficiency in the causation of other degenerative diseases and to the need of specific vitamin treatment if treatment is to be effective and scientific.

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## SULFATHIAZOLE IN THE TREATMENT OF PNEUMOCOCCUS PNEUMONIA.

### COMPARATIVE STUDY UTILIZING SULFAPYRIDINE THERAPY.

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THE preparation of therapeutically effective synthetic derivatives of sulfanilamide has been demonstrated by the conjugation of sulfapyridine. The possibility of further compounds is illustrated

by the report of Fosbinder and Walter<sup>4</sup> who describe several new sulfanilamide derivatives, among which is sulfathiazole. This preparation was independently synthesized by Lott and Bergeim.<sup>7</sup> Sulfathiazole (2-para-amino benzene sulfonamide thiazole) is apparently readily absorbed from the gastro-intestinal tract, thus resembling sulfanilamide rather than sulfapyridine. The studies of the blood level concentration and the urinary secretion also simulate the action of sulfanilamide, in that high blood levels are quickly attained and excretion in the urine occurs at a rapid rate. The degree of conjugation in both the blood and urine is much less than that which occurs with sulfapyridine. As a consequence, a larger percentage of the total drug absorbed into the blood stream is therapeutically active. Chemotherapeutically considered, acetylated sulfanilamide compounds are inert.

The preliminary studies have indicated that sulfathiazole equals sulfapyridine in therapeutic effectiveness when comparative studies were made with various types of experimental pneumococcus infections. On the other hand, staphylococcus infections respond more readily to sulfathiazole medication. However, because of the paucity of available published reports, the evaluation of the effectiveness and toxicity of sulfathiazole must await further clinical and experimental data. This clinical study presents a contribution to such data.

**Method of Study.** The dosage of sulfathiazole consisted of 4 gm. (8 tablets) initially followed by 1 gm. every 4 hours, day and night, until the temperature remained normal for 48 hours when medication was discontinued. Thirty-five patients received 4 gm. initially followed by dosages of 3 gm., 2 gm. and then 1 gm. at the subsequent 4-hour intervals respectively. The blood levels were not appreciably affected by this procedure. Serum was not combined with sulfathiazole nor is the use of intravenous sodium sulfathiazole here reported. Proved typed pneumococcus pneumonias with physical signs and positive Roentgen ray evidence are reported in this study. Thorough routine investigation included blood counts, blood cultures, urinalysis, with the blood sulfathiazole determinations computed after 24 hours of drug regimen. Adjunct therapeutic measures were utilized such as oxygen, intravenous fluids, and other drugs. It must be stated that these accessory methods were infrequently employed. For example, oxygen was used in only 5 cases. The attempt was thus made to evaluate the drug alone under severe clinical conditions. The clinical material was unselected in a large charity hospital. A contemporary comparative study included a series of patients treated with sulfapyridine alone, or combined with immune serotherapy. The age, sex, types of pneumococci, bacteremic incidence and contemporary time occurrence in this sulfapyridine series furnish practically an alternate case control study for sulfathiazole.

**Results.** This report comprises 169 patients treated by peroral sulfathiazole. Table 1 illustrates the results obtained in the individual types of pneumococcus infections. The deaths in the total series of 169 patients were 9 in number (5.3%). Of the non-bacteremic group in this series 7 died (4.8%). Twenty-four posi-

tive blood cultures were encountered, an incidence of 14.2% in the entire series; there were 2 deaths in this group (8.3%). The bacteremic investigation was interrupted for 18 patients because of the lack of supply of available culture medium for several days. Several positive cultures would undoubtedly have resulted. Nevertheless,

TABLE 1.—SULFATHIAZOLE-TREATED PATIENTS.

Type.	Total.			Non-bacteremic.			Bacteremic.		
	No. of cases.	Deaths.		No. of cases.	Deaths.		No. of cases.	Deaths.	
		No.	%.		No.	%.		No.	%.
I . . . . .	27	3	11.1	19	2	10.5	8	1	12.2
II . . . . .	75	3	4.0	62	3	4.8	13	0	0
III . . . . .	19	3	15.8	18	2	11.1	1	1	100
IV . . . . .	8	0	0	8	0	0	0	0	0
V . . . . .	6	0	0	6	0	0	0	0	0
VII . . . . .	15	0	0	14	0	0	1	0	0
VIII . . . . .	13	0	0	13	0	0	0	0	0
XIV . . . . .	1	0	0	0	0	0	1	0	0
XIX . . . . .	1	0	0	1	0	0	0	0	0
XXI . . . . .	1	0	0	1	0	0	0	0	0
XXV . . . . .	2	0	0	2	0	0	0	0	0
XXVII . . . . .	1	0	0	1	0	0	0	0	0
Total . . . . .	169	9	5.3	145	7	4.8	24	2	8.3

Incidence of bacteremia, 14.2%.

TABLE 2.—SULFAPYRIDINE AND SULFAPYRIDINE COMBINED WITH SERUM.

Type.	Total.			Non-bacteremic.			Bacteremic.		
	No. of cases.	Deaths.		No. of cases.	Deaths.		No. of cases.	Deaths.	
		No.	%.		No.	%.		No.	%.
I . . . . .	37	0	0	33	0	0	4	0	0
II . . . . .	61	4	6.5	49	2	4.1	12	2	16.6
III . . . . .	14	0	0	13	0	0	1	0	0
IV . . . . .	10	0	0	9	0	0	1	0	0
V . . . . .	4	0	0	4	0	0	0	0	0
VII . . . . .	14	2	14.2	11	1	9.1	3	1	33.3
VIII . . . . .	9	0	0	8	0	0	1	0	0
IX . . . . .	1	0	0	1	0	0	0	0	0
X . . . . .	1	1	100	1	1	100	0	0	0
XV . . . . .	1	0	0	1	0	0	0	0	0
XVII . . . . .	1	0	0	1	0	0	0	0	0
XVIII . . . . .	1	0	0	0	0	0	1	0	0
XIX . . . . .	1	0	0	0	0	0	1	0	0
XX . . . . .	2	0	0	2	0	0	0	0	0
XXIII . . . . .	5	0	0	5	0	0	0	0	0
XXV . . . . .	1	0	0	1	0	0	0	0	0
XXVII . . . . .	1	0	0	1	0	0	0	0	0
Total . . . . .	164	7	4.2	139	4	2.8	25	3	12

Incidence of bacteremia, 15.2%.

these 18 are included in the non-bacteremic group. There were 63 patients (38%) over 40 years of age. Eight of the 9 deaths occurred in patients beyond 40 years. The contemporary sulfapyridine-treated series which included 69 serum combinations totaled 164 patients with 7 deaths, a percentage of 4.2; there were 4 deaths (2.8%) in 139 non-bacteremic cases, while of 25 patients with posi-

tive blood cultures 3 died (12%). The bacteremic incidence was 15%. Table 2 summarizes the results for the various types of pneumococci. There were 71 patients (43%) over 40 years of age in the sulfapyridine series. Three of the total of the 7 deaths were encountered in this age group.

**Blood Concentration of Sulfathiazole.** Sulfathiazole appears rapidly in the blood stream following oral administration. The blood levels are relatively high when compared to sulfapyridine, averages well over 6 mg. per 100 cc. being readily attained. These levels are not as constantly maintained, greater variations occurring on the maintenance dose than with sulfapyridine. For example, in the daily blood determinations on B. W. from April 23 to 29, 1940 inclusive, the readings were 9, 7, 5, 5, 3, 5, 2, 8 and 4 mg. per 100 cc. respectively. The initial determination (9 mg. per 100 cc.) was made 19 hours after the onset of medication. Thirty-six hours after the drug was discontinued no traces of the drug were found in the blood or urine. The drug is eliminated rapidly from the blood stream, clearing frequently within 24 hours after drug cessation. The drug similarly disappears from the urine in 24 to 36 hours. The conjugated form constitutes a very small fraction of the total blood content. An analysis of 100 determinations showed an average of only 4% conjugation in the total blood sulfathiazole. The acetylated fraction of the total sulfathiazole content in the urine similarly is very much less than occurs with sulfapyridine. The analysis revealed an average of 13% conjugation in the urine. While it is difficult to correlate clinical response to a definite blood concentration of the drug, 6 mg. per 100 cc. seems an apparently satisfactory level in the light of our experience.

**Untoward Effects of Sulfathiazole.** Seven patients experienced nausea and vomiting, 1 requiring cessation of the drug. No evidence of renal irritation, gross or microscopic hematuria, anuria or nitrogen retention could be attributed to the drug in this clinical experiment. Similarly, no marked effect was induced on the hemopoietic system. Hemolytic anemia was not encountered. Liver damage clinically was not found. Drug fever and drug rashes appeared. Five patients, 2 of whom succumbed, developed a drug rash diffusely distributed on the face and extremities; 3 were in the form of dark red nodules, 0.5 to 1 cm. in diameter, distinctly elevated and very firm. All 5 patients were very ill and had high temperatures. Two developed an erythema multiforme type of eruption. Two had, in addition to the rash, an intense conjunctivitis. The 3 patients who survived had received 20, 30, and 16 gm. respectively of the drug, while the 2 fatal cases had taken 30 and 75 gm. respectively. The blood levels ranged from 5 to 10 mg. per 100 cc. One additional instance of marked conjunctivitis was noted. While the toxic reactions encountered are similar to those experienced with sulfanilamide and sulfapyridine, the comparative

toxicity approaches sulfanilamide in that the reactions are distinctly less frequent and milder.

**Complications.** Empyema has been a relatively frequent complication this season, encountered on all therapeutic regimens. Seven patients developed empyema in the sulfathiazole-treated group,

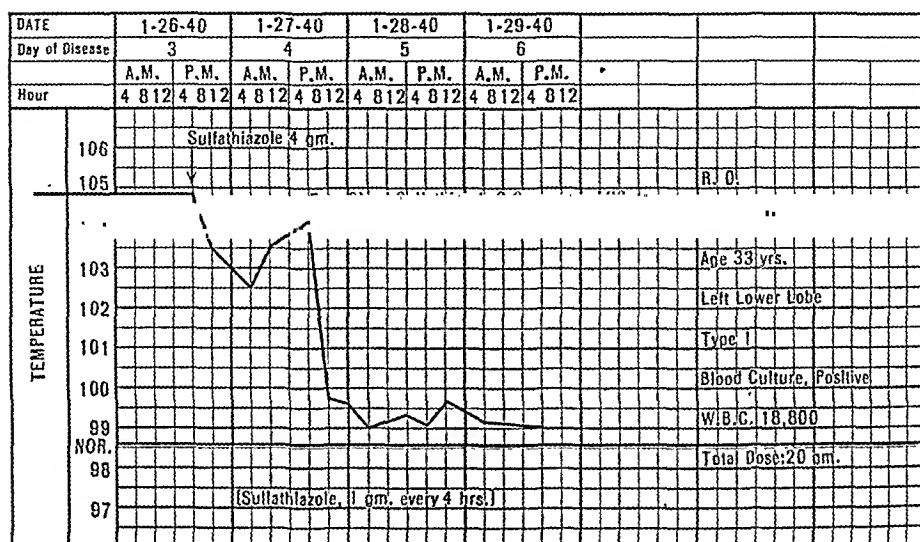


CHART I.

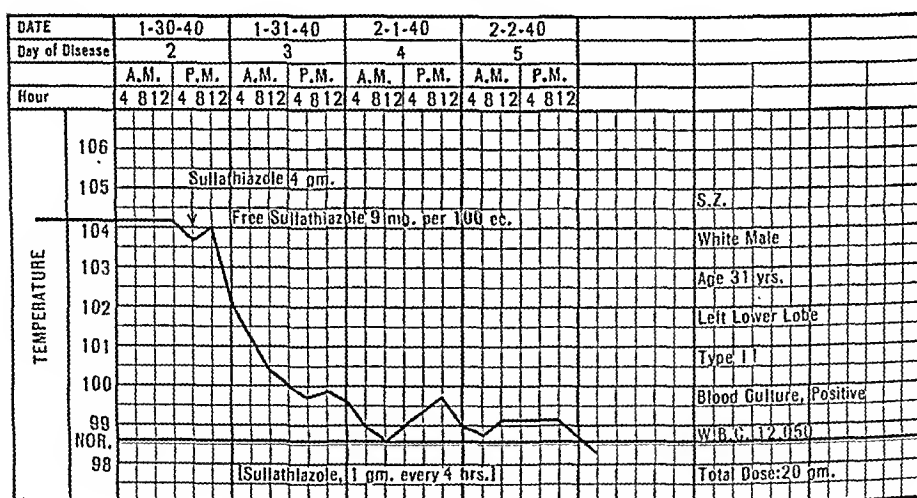


CHART II.

while 4 occurred in the sulfapyridine series. Three sterile effusions developed. One patient showed a pericarditis. Two instances of delayed resolution were noted. The sulfathiazole group is remarkably free from pyogenic complications such as otitis media, mastoiditis, endocarditis and meningitis.

**Comments.** The satisfactory clinical response to sulfathiazole in pneumococcus pneumonia is revealed by the course of the temperature curve. This shows a characteristic combination of crisis and lysis without the precipitous termination of the former and the absence of the prolonged course of the latter. This may be described as a concave trajectory curve, or geometric hyperbola with the normal temperature level attained in the 48- to 60-hour period.

Charts 1 and 2 are characteristic of the termination described and contain the essential pertinent data, illustrating the effect in a Type I and Type II bacteremic infection respectively. Table 3 compares the hour period in which the temperature reached and remained at the normal level, following the onset of medication.

TABLE 3.—NORMAL TEMPERATURE FOLLOWING ONSET OF MEDICATION.

Hours.	Sulfathiazole.		Sulfapyridine.		Sulfapyridine combined with serum.	
	No.	%.	No.	%.	No.	%.
24 . . . . .	60	37.4	39	40.6	21	34.4
48 . . . . .	59	36.9	41	42.7	28	45.9
72 . . . . .	16	10.0	6	6.2	2	3.2
More than 72 . .	25	15.6	10	9.6	10	16.2
Totals . . .	160		96		61	

The comparison includes sulfathiazole, sulfapyridine, and sulfapyridine combined with immune serotherapy. Temperature reduction is produced more rapidly by the sulfapyridine therapy, although the differences are not pronounced. Comment must be made of the clinical impression created by the patient with pneumonia treated with sulfathiazole. When comparison with sulfapyridine therapy is made, the relative comfort of the patient on sulfathiazole, the absence of vomiting and the greatly diminished indication for parenteral fluids stand out prominently.

**Summary and Conclusions.** The following quotation from Long<sup>6</sup> is both timely and necessary: "The evaluation of these new chemotherapeutic compounds will necessitate extensive experimental and clinical investigations in order to determine their efficiency in the control of infections and their clinical toxic manifestations. Until the time when such data are in hand, it is hoped that enthusiasm does not outrun common sense."

1. One hundred and sixty-nine patients with typed pneumococcus pneumonia were treated with peroral sulfathiazole with 9 deaths, a 5.3% mortality.

2. A control series in which sulfapyridine combined with serum was utilized shows slightly better results, namely a 4.2% mortality, although the mortality in the bacteremic group was higher with sulfapyridine treatment.

3. Sulfathiazole is apparently equally as effective a therapeutic agent as sulfapyridine in the treatment of pneumococcus pneumonia.

4. Sulfapyridine showed more effectiveness in the therapy of Type I and Type III infections, whereas sulfathiazole produced better results in infections by Types II and VII.

5. Nausea and vomiting and the other common toxic manifestations of sulfapyridine therapy are much less frequent with sulfathiazole.

6. Drug fever and especially the papulonodular eruption with conjunctivitis are severe toxic manifestations of sulfathiazole medication.

7. The blood concentration level varies considerably in the same individual on the ordinary maintenance dose of 1 gm. every 4 hours.

The Squibb Institute for Medical Research, New Brunswick, N. J., kindly provided the sulfathiazole for use in this investigation.

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### SULFATHIAZOLE TREATMENT IN RESPIRATORY INFECTIONS.

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DURING the winter of 1939-1940, 52 cases of respiratory infection seen at the University and Graduate Hospitals of the University of Pennsylvania were treated with sulfathiazole. In each of these cases there was an initial diagnosis of pneumonia. In all cases specimens of sputum were examined for pneumococci and in the great majority chest Roentgen rays were obtained and blood cultures were taken before treatment was started. There were 34 white patients and 18 colored, 25 male patients and 27 female. The majority fell in the age group of 15 to 40 although there were 11 over 50 years.

Thirty-seven turned out to be typical cases of pneumococcal pneumonia. In 6 of these there were positive blood cultures. The

type of pneumococci encountered are shown in Table 1. It will be noted that 13, or one-third of the group, fall in the first three types. This fact plus the high incidence of blood stream infection is good evidence of the severity of the type of infection.

TABLE 1.—TYPES OF PNEUMOCOCCI.

	Cases.			Cases.	
1 . . . . .	8	8	. . . . .	5	
2 . . . . .	1	14	. . . . .	1	
3 . . . . .	4	17	. . . . .	1	
4 . . . . .	3	18	. . . . .	2	
5 . . . . .	5	19	. . . . .	1	
6 . . . . .	1	33	. . . . .	3	
7 . . . . .	3				

There were 11 cases of atypical or bronchial pneumonia. In 3 cases pneumococci were found in the sputum. In 2 others *Strep. viridans* was found and in 1 a non-hemolytic streptococcus. In the remainder no predominant organisms were found. There were no cases with positive blood cultures in this group.

In 4 cases the final diagnosis was bronchitis because of negative chest Roentgen rays and the paucity of chest signs on physical examination. In 3 cases the predominant organism in the sputum was a pneumococcus and in the fourth a *Strep. viridans* was found. The types of pneumococci found were 4, 8 and 33.

*Dosage.* An initial dose of 3 gm. of sulfathiazole (by mouth) was given, followed by a second dose of 3 gm. in 4 hours. Then 1 gm. was given every 4 hours until treatment was discontinued. In general, therapy was continued for 2 or 3 days after the temperature had fallen to normal.

Antipneumococcic serum was not withheld if at the end of 24 to 48 hours there had not been clinical improvement. Serum was given in 4 of the typical pneumococcal pneumonias, 3 of whom died and in 2 of the atypical pneumonia patients both of whom were fatalities.

*Results.* Of the 37 patients with typical pneumococcic pneumonia, 2 died, giving a mortality rate in this small group of 5.4%. These same 2 deaths were also the only fatalities among the 6 cases with blood stream invasion. Of the remaining 4 cases with positive blood cultures that recovered, 2 had both serum and sulfathiazole. One of these last 2 had a severe Type 1 infection and was not improved after 24 hours of sulfathiazole therapy. The other patient had developed a positive blood culture while taking sulfapyridine and was then shifted to sulfathiazole in large dosage without improvement. An empyema occurred while on sulfathiazole but he eventually recovered perhaps in spite of both drugs as the infecting organism, a Type 4 pneumococcus, was found to be highly resistant to both sulfapyridine and sulfathiazole in *in vitro* experiments.

The temperature fell to normal in 24 hours in 16 patients and in 48 hours in 12 others. In 6 cases the temperature did not reach normal for 96 hours. A secondary rise in temperature occurred in



8 cases after the temperature had been normal for 24 hours. In 1 case this secondary rise was caused by drug fever, in another by a complicating thrombophlebitis but in the other 6 no etiologic cause was determined. The 1 case of thrombophlebitis which occurred on the eighth day of treatment and an empyema which cleared up on chemotherapy and thoracentesis constituted the only complications to the pneumococcic infection.

**Clinical Abstracts of Fatal Cases.** CASE 1.—A. S., 63-year-old white male, admitted to the University Hospital on the sixth day of his illness. On examination his temperature was 102.4° F., pulse 118 and respirations 44. Chest Roentgen ray showed density of the right upper and lower lobes and the left upper lobe. A Type 1 pneumococcus was recovered from the sputum. The white blood count was 9800 with 94% neutrophils.

On the second hospital day the blood culture taken on admission was reported as showing 130 colonies of Type 1 pneumococcus per cc. of blood. Another blood culture was taken at once and later the patient was given 200,000 units of Type 1 antipneumococcic rabbit serum. This second blood culture taken before the serum therapy and after 24 hours of sulfathiazole therapy showed growth only in the flasks; the plates were sterile. On the fifth hospital day the blood culture was negative and although the temperature did not go above 99.4° F., the patient did not appear clinically improved. Serum was again given 2 days later and in spite of continued sulfathiazole therapy the temperature rose to 102° F., the patient became weaker; the lungs filled with fluid and the patient died.

CASE 2.—F. B., a 58-year-old colored man, admitted to the Graduate Hospital on the second day of his disease. He gave a past history of hypertension and asthma. Examination disclosed an elderly appearing colored man in acute distress. The temperature was 101.6° F., pulse 120, and respirations 40. Physical examination and Roentgen ray showed involvement of the right lower lobe and part of the right middle lobe. Laboratory studies revealed a Type 8 pneumococcus in the sputum, 4.3 millions red blood cells, 66% hemoglobin and 8000 white blood cells with 85% neutrophils. The Wassermann reaction was 4+.

After 2 days with but little improvement the sulfathiazole was increased to 12 gm. per day and 200,000 units of Type 8 pneumococcic antisera were given. The blood level of sulfathiazole as run by the inadequate methods available (*vide* next paper) was 2.2 mg. per 100 ml. after the first 24 hours but rose to 17 mg. per 100 ml. on the 12 gm. per day dose and was 10.5 mg. for 100 ml. the day before death.

Twenty-four hours before the patient died (on the ninth hospital day) he appeared fairly well and his temperature, pulse and respiration were down. In 6 hours, however, he relapsed, developed peripheral circulatory collapse and died. The total sulfathiazole dose was 66 gm.

At autopsy the important findings were: an acute, severe hemorrhagic gastritis, consolidation of the right upper lobe, the right lower lobe and part of the right middle lobe, cloudy swelling of the liver, luetic aortitis and early nephrosclerosis. There were no crystalline deposits in the kidneys or urinary passages.

In the group of 11 atypical pneumonias 3 patients died. There were no cases with positive blood culture. The temperature fell to normal in 8 of the cases within 24 hours. There were no complications.

CASE 3.—L. K., a 68-year-old white male with diabetes and cancer of the bladder, suddenly developed a temperature of 104° F., pulse 114, respirations 30, while in the University Hospital. Physical examination and Roentgen ray disclosed a consolidation of the left lower lobe of the lung. Examination of the sputum revealed a predominance of *Strep. viridans* and a moderate number of hemolytic *Staph. aureus*. The blood count showed 3.4 million red blood cells, 60% hemoglobin and 14,000 white blood cells with only 55% neutrophils. The blood culture was negative.

After apparently improving, the temperature not going over 99.8° F. on the seventh day of illness, a toxic erythema and edema of the back of the hands occurred on the tenth day and the temperature rose to 104.2° F. On the eleventh day the drug having been discontinued after a total of 50 gm. the temperature remained normal. Three days later, the temperature again rose and the patient died. The blood level was 6.7 mg. per 100 ml. on the second day of treatment and 4.6 mg. per 100 ml. on the ninth day.

CASE 4.—C. K., a 53-year-old white male was being prepared for operation for cancer of the lung at the University Hospital. He suddenly became acutely ill with a temperature of 104° F., pulse 120 and respirations 38. Physical examination disclosed consolidation of the right upper lobe and right middle lobe. A Type 22 pneumococcus was recovered from bronchoscopic drainage. The blood count showed 3.4 millions red blood cells, 69% hemoglobin, 22,100 white blood cells with 92% neutrophils.

Sulfathiazole was started in the usual dosage and 100,000 units of Type 22 pneumococcic antiserum were given daily for 3 days. On the third day the blood culture was reported as positive for Type 18 pneumococcus. Of Type 18 antiserum, 100,000 units were therefore given and repeated for 3 days.

The temperature fell by crisis on the fourth day of the disease and remained practically normal for 2 days. It then rose rapidly and the patient died on the ninth day. The sulfathiazole was stopped on the seventh day after red blood cells and sulfathiazole crystals were found in the urine. The total dose was 35 gm.

At autopsy a bronchogenic carcinoma of the right main bronchus of the lung was found with massive secondary lesions of the liver. There were multiple abscesses of the right lung with bronchopneumonia and pyopneumothorax. The kidneys were not examined.

CASE 5.—M. H.,<sup>4</sup> white female, aged 77, had had a chronic cough for 6 months associated with slight dyspnea on exertion for 3 months prior to admission. Two weeks before admission her cough became worse and she was referred to the University Hospital with a diagnosis of pneumonia. Examination revealed an acutely ill woman with a temperature of 102.6° F., dyspnea and slight cyanosis. There were physical signs of involvement of both lower lobes. Roentgen ray showed density of the entire left chest and the right lower lobe. A Type 3 pneumococcus was recovered from the sputum. The blood culture was negative. The white blood count was 15,600 with 90% neutrophils.

A diagnosis of atypical pneumonia was made and sulfathiazole given in the usual dosage. Intractable nausea and vomiting ensued which lasted until the medication was discontinued at the end of the fourth day. Daily parenteral infusions of saline and glucose were given. On the third day abundant albumin was found in the urine and on the fourth day there was still abundant albumin plus the additional discovery of microscopic hematuria. It was also felt that the urinary output was falling so that the sulfathiazole medication was discontinued after a total of 24 gm. had been given.

On the fifth hospital day all the urine passed was obtained by catheter.

The amount totalled 160 cc. Albumin was abundant and there were many hyaline and granular casts. On the sixth day the total urine output consisted of 225 cc. obtained by catheter. On the eighth day the urinary output had risen to 575 cc. but the patient was clinically worse so that 100,000 units of Type 3 antipneumococcus rabbit serum were given. Two days later after a short period of improvement the patient suddenly died.

*Necropsy* (salient features only). Both kidneys (160 gm. each) were large and soft. The cortices were narrowed, finely granular and pale reddish-pink in color. The pyramids were large and contained small hemorrhages and prominent streaks of "gritty" crystalline material which converged at the apices and extended into the calices as short fragile cords. Gritty sandlike material was found in the pelvis and urinary bladder. On analysis this gritty material was composed of a derivative of sulfathiazole. The lungs showed marked peribronchial and perivascular fibrosis and a mild degree of bronchopneumonia. There was an acute hemorrhagic pancreatitis and a patent foramen ovale.

The group of 4 patients with bronchitis, 3 pneumococcol, is worth mentioning because of the uniformly good results. The temperature fell abruptly to normal in 24 hours in each case and there was marked improvement in the clinical condition coincident with this fall.

*Toxicity.* The various toxic reactions and their incidence are shown in Table 2. It will be noticed that vomiting occurred in only 8 of the entire group of cases and in only 1 of the 8 was this severe in nature. Microscopic hematuria was present in 4 patients and crystals of sulfathiazole or acetyl sulfathiazole were found in the urine of 12. One patient (M. H.), previously reported<sup>4</sup> in greater detail, was found at autopsy to have concretions of acetyl sulfathiazole within the collecting tubules of the kidneys.

TABLE 2.—TOXIC REACTIONS WITH SULFATHIAZOLE.

	Typical group. 6 (1 severe)	Atypical group. 2
Vomiting . . . . .		
Urine—		
Renal concretions with oliguria (autopsy) .	0	1
Crystals . . . . .	10	2
Microscopic hematuria . . . . .	2	2
Dermatitis . . . . .	0	3
Headache . . . . .	2	0
Psychologic difficulties . . . . .	1	0
	(depressed)	
Conjunctivitis . . . . .	1	0
Fever (drug) . . . . .	1	0
Icterus . . . . .	1	0
	(4th day of treatment— urobilinogen 1 to 50)	

Three patients developed a toxic dermatitis. This took the form of a lesion very closely simulating erythema nodosum. The eruption tended to be bilaterally symmetrical and on the extensor surfaces of the arms and legs. One patient developed toxic conjunctivitis such as described by Haviland and Long.<sup>3</sup> One patient was noticed to be slightly icteric on the fourth day of treatment

and was found to have a positive test for urobilinogen in the urine in a dilution of 1 to 50. There was little or no fall in red count or hemoglobin.

**Discussion.** Our results in this small series of cases closely approximate those described by others.<sup>1,5,6</sup> Sulfathiazole given in slightly larger doses than sulfapyridine effects cure in pneumonia in about the same percentage of cases as does sulfapyridine. The temperature does not fall quite so abruptly perhaps, with sulfathiazole as with sulfapyridine, but this fact is overshadowed by the great reduction in the incidence of nausea and vomiting with the use of sulfathiazole. It is interesting to note that all of our fatalities were among the 11 patients over 50 years of age. This gives a perfect record for cures in the other 41 patients and a mortality rate of 45% in the cases over 50 years of age. This emphasizes a very important point. The fatalities in adequately treated pneumonia do not occur in the young, healthy individuals but in the debilitated, elderly patient with complicating disease. All 5 of our patients who died improved temporarily under treatment but later relapsed. In 4, there were complicating disease conditions present. Case F. B. had hypertension, asthma and syphilis; L. K. had diabetes and cancer of the bladder; C. K. had cancer of the lung with metastasis to liver; and M. H. had congenital heart disease and marked pulmonary fibrosis.

In both drugs, the greatest danger appears to lie in the re-crystallization of the free, or, more frequently, the acetylated drug within the urinary passages. With sulfapyridine this crystallization occurred most frequently within the renal pelves and ureters. Sulfathiazole, however, perhaps due to the fact that it is not reabsorbed in the collecting tubules crystallizes out both in the experimental animal<sup>2</sup> and man within the renal tubules. Fortunately, sulfathiazole is not acetylated to as large an extent as sulfapyridine for, although pure sulfathiazole is almost twice as soluble as pure sulfapyridine, the acetylated forms of both drugs are very insoluble. There is certain evidence that by giving alkalis (*vide* next paper) with these drugs the danger of urinary concretions is lessened. Certainly in the majority of our cases it seemed possible to control the crystalluria by increasing fluid intake and giving sodium bicarbonate. However, in view of the small differences in solubility of the acetylated sulfathiazole crystals in the range of pH found in urine, it is probable that the reduction in numbers of crystals was due more to the increased fluid intake.

We feel, therefore, that the best means of avoiding the renal complications from either sulfathiazole or sulfapyridine consists in an adequate fluid intake, at least 2500 cc. a day, parenterally if necessary, giving an alkali, sodium bicarbonate or sodium lactate, keeping an accurate intake-output chart, and daily urinalyses particularly during the first few days of treatment.

**Summary.** Fifty-two cases of respiratory infection were treated with sulfathiazole. There were 37 cases with typical pneumococcic pneumonia with 2 deaths (a mortality of 5.4%), 11 cases of atypical pneumonia with 3 deaths, and 3 cases of pneumococcic bronchitis, all with prompt improvement. The toxic reactions of sulfathiazole are discussed.

We wish to thank E. R. Squibb & Sons for supplying us with the sulfathiazole used in this study.

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### SULFATHIAZOLE IN BLOOD AND URINE.

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IN view of the recognized value of sulfathiazole as a chemotherapeutic agent, it would seem desirable to ascertain optimal levels of concentration at which this drug might be maintained in the circulation. The methods currently employed for the analysis of sulfathiazole in blood are recognized as inadequate,<sup>5a,8,9</sup> since recovery of the drug when added to whole blood is uniformly low. In this paper we wish to report observations regarding the difficulties encountered in the analyses and to offer a procedure of analysis applicable for clinical purposes. Moreover, since the greatest danger in the use of the drug appears to be the occurrence of crystalline concretions in the urinary passages,<sup>1,3,4,8-10</sup> studies are reported relating to the excretion of the drug in urine, its solubility, and crystal structure.

**Recovery of Sulfathiazole Added to Whole Blood, Serum and Normal Urine, Respectively.** The addition of sulfathiazole to whole blood to give samples containing 5 to 15 mg. per 100 ml. yielded in 18 duplicate analyses an average of 86.4% recovery. The analyses were made by applying the Marshall and Litchfield method<sup>7</sup> for determination of sulfanilamide to the measurement of sulfathiazole.\*

\* It should be noted that Bratton and Marshall<sup>6</sup> at the time of their publication advised caution in applying the method for the determination of sulfanilamide to other sulfonamide preparations that might be used therapeutically at a later time.

The diminutions in recovery were obtained whether diazotization and coupling were carried out in an ice bath or at room temperature; whether N-(1-naphthyl)-ethylenediamine or dimethyl- $\alpha$ -naphthylamine was used as the coupling component; or whether oxalated, citrated, or defibrinated blood was employed. Treating the protein-free filtrates of the prepared whole blood samples with 0.5 N HCl and heating in a boiling water bath for 1 hour did not alter the percentage of sulfathiazole that was recovered.

In several series of analyses sulfathiazole was added to the blood before precipitation of the proteins and to the filtrates after precipitation of the proteins. A comparison of the results of these determinations indicated that although approximately 14% of the drug was lost when it was added to whole blood, practically complete recovery was obtained when the drug was added to blood filtrates after protein precipitation. Since the loss of sulfathiazole occurred during the precipitation of proteins with trichloroacetic acid, other protein precipitants were investigated. A list of the protein precipitants studied is given in Table 1, together with the percentages of recoveries obtained. It will be seen that all of the protein precipitants that were tried yielded unsatisfactory recovery of the drug.

TABLE 1.—RECOVERY OF SULFATHIAZOLE USING VARIOUS PROTEIN PRECIPITANTS.

Precipitant.	Percentage recovery (average of 6 or more analyses).
Trichloroacetic acid . . . . .	86
Heat and trichloroacetic acid . . . . .	89
Tungstic acid . . . . .	59
Metaphosphoric acid . . . . .	72
Toluenesulfonic acid . . . . .	81
Alcohol-acetone . . . . .	85
ZnSO <sub>4</sub> -NaOH . . . . .	Unsatisfactory*
Ethyl alcohol . . . . .	Unsatisfactory†

\* Color development was poor.

† Turbidity in the filtrates on diazotization and coupling was not entirely eliminated.

Sulfathiazole was added to samples of blood serum to obtain final concentrations of 5 to 30 mg. per 100 ml. of blood serum. With dimethyl- $\alpha$ -naphthylamine as the coupling reagent the amounts of sulfathiazole recovered varied from 95% to 99% of the theoretical content (average, 97%). The values given in Table 2 are characteristic of several series similarly analyzed.

TABLE 2.—RECOVERY OF SULFATHIAZOLE ADDED TO BLOOD SERUM.

Sulfathiazole in serum, mg. per 100 ml.	Sulfathiazole recovered, mg. per 100 ml.	Per cent recovery.
5.00	4.83	96.5
10.00	9.90	99.0
20.00	19.40	96.9
30.00	28.90	96.4

**Procedure of Analysis.** Since the recovery of sulfathiazole from serum is within approximately 3% of the theoretical, we have preferred routinely to perform our analyses on serum and to make an arbitrary correction for the loss encountered. The method that we have finally adopted for the analysis of sulfathiazole in serum is essentially an adaptation of the Marshall and Litchfield procedure<sup>7</sup> for the determination of sulfanilamide in whole blood.

*Procedure:* 2 ml. of serum\* obtained from centrifuged clotted blood are run into a 25-ml. volumetric flask containing 10 ml. of 8% trichloroacetic acid. After shaking thoroughly to keep the precipitate finally divided, the solution is diluted to the mark with distilled water. The contents are mixed and allowed to stand for 20 minutes; then filtered through Whatman No. 44 paper to obtain a clear, colorless filtrate. Ten milliliters of the filtrate are diazotized at room temperature with 1 ml. of a 0.1% freshly made solution of sodium nitrite. The solution, after standing for 3 minutes, is treated with 1 ml. of an 0.5% solution of ammonium sulfamate†. After mixing thoroughly, 5 ml. of di-methyl- $\alpha$ -naphthylamine‡ coupling reagent are added; the tube is stoppered, inverted once, and allowed to stand for 10 minutes.

Comparisons of color development are made by means of a colorimeter (or photoelectric cell device) utilizing sulfathiazole standards of appropriate concentrations carried through the same procedure as with the unknown. It is important that the solutions be well shaken before placing them into the colorimeter cups to eliminate small gas bubbles that may be present. (The gas is presumably nitrogen formed by the destruction of  $\text{HNO}_2$  with  $\text{NH}_2\text{SO}_3\text{NH}_4$ ). For our purposes we employ a colorimeter (Bausch & Lomb) having an attachable lamp. The eyepiece of the colorimeter is fitted with a No. 74 Wratten filter. Standards of appropriate concentrations are made from a stock solution of sulfathiazole containing 200 mg. per liter. It is convenient to have prepared standards having concentrations of sulfathiazole of 0.2, 0.4 and 0.8 mg. per 100 ml., respectively.

Calculation:

$$\frac{\text{Reading of Standard}}{\text{Reading of Unknown}} \times \text{mg. of sulfathiazole in standard} \times \text{Dilution Factor} \times \text{Correction Factor} = \text{mg. per 100 ml.}$$

Correction factor = 1.03.

Recovery of sulfathiazole from protein-free urine is practically quantitative. The procedure for serum may be applied to urine determinations disregarding the correction factor. It is preferable that appropriate dilutions of urine be made so that sulfathiazole concentration in the diluted urine is between 5 and 30 mg. per 100 ml.

**Recovery of Acetylsulfathiazole Added to Whole Blood, Serum, and Normal Urine, Respectively.** Acetylsulfathiazole was added to blood, blood serum and urine in concentrations of 5 to 20 mg. per 100 ml., as in experiments with the parent compound. In these determina-

\* In blood serum containing high concentrations of sulfathiazole, 1 ml. of serum is employed.

† Marshall and Litchfield<sup>7</sup> recommend that the solution of ammonium sulfamate be buffered with sodium dihydrogen phosphate in order to increase the rate of coupling. In our experience the addition of the buffer has not proved necessary.

‡ Solution contains 1 ml. dimethyl- $\alpha$ -naphthylamine in 250 ml. of 95% ethyl alcohol.<sup>8b</sup>

tions 10 ml. of the protein-free filtrate were first heated with 0.5 ml. of 4 N hydrochloric acid in a boiling water bath for 1 hour; then cooled, and the volume readjusted to 10 ml. with distilled water. The procedure followed was the same as that employed in determining the free form, excepting that comparisons were made with standards containing acetylsulfathiazole subjected to hydrolysis instead of sulfathiazole.

When acetylsulfathiazole was added to whole blood the percentage of recoveries in 6 or more duplicate analyses averaged 79%; when added to blood serum, 86%; and to normal urine, 99.6%. The magnitude of the loss in both whole blood and serum would seem to preclude the use of the method for the conjugated form.

**The Solubility of Sulfathiazole and Acetylated Sulfathiazole in Phosphate Solutions and in Samples of Buffered Normal Urine at Various Physiologic pH Concentrations.** Solubility measurements of sulfathiazole and acetylsulfathiazole were made in dilute phosphate buffer solutions\* of pH concentration from 5.6 to 8. An excess of these compounds was suspended in prepared buffer solutions, agitated and kept in a water bath at 38° C. for approximately 2 hours. The solutions were filtered and analyses for total sulfathiazole were made on the filtrates. Since presence of extraneous material may influence the true solubility of a component, similar measurements of solubility were made on urines adjusted to a pH range of 5.6 to 8.

Solubility Curves of Sulfathiazole and Acetylsulfathiazole

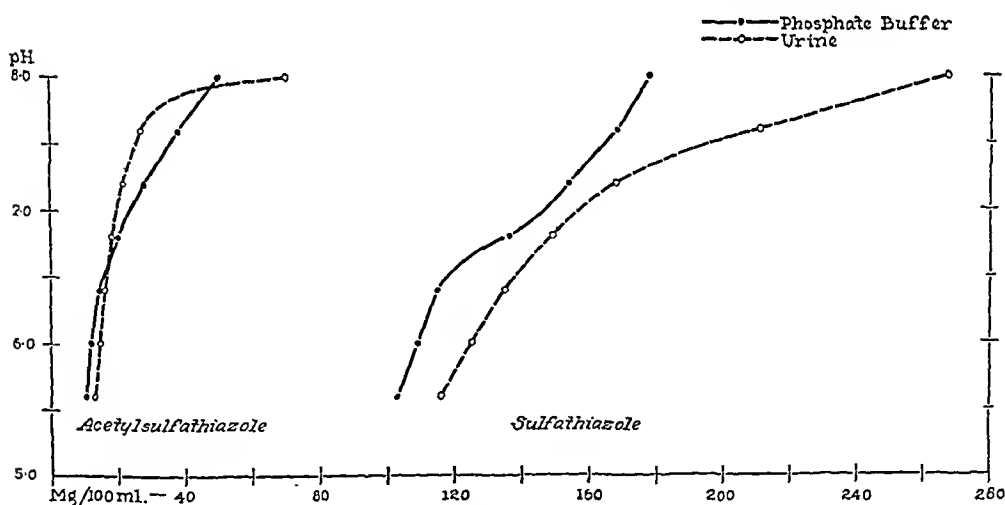


FIG. 1

In Figure 1 the curves are given showing the concentration of sulfathiazole and acetylsulfathiazole in aqueous solutions within the pH range indicated. Each curve represents a composite of three

\* The solutions were made by diluting appropriate mixtures of  $\text{Na}_2\text{HPO}_4$  and  $\text{KH}_2\text{PO}_4$ , 1 part to 10 parts of distilled water.



sets of determinations. It will be seen that the solubility of sulfathiazole in urine and in dilute phosphate solutions does not vary greatly. The same close agreement is observed in the solubility of acetylsulfathiazole in urine and dilute phosphate solutions. Acetylsulfathiazole is shown to be only about one-tenth as soluble as sulfathiazole.

The data concerning the solubility of these compounds support the clinical observations that the occurrence of crystalline concretions in the urine appear to be lessened when the volume of urine is increased by an adequate ingestion of water and its reaction is made alkaline.

**The Crystalline Structure of Sulfathiazole and Its Acetyl Derivatives.** In our experience the most common type of crystal found in the urine of patients receiving sulfathiazole has been a dumb-bell shaped structure (Fig. 2). Occasionally, rosette and large orthorhombic hemimorphic crystals are also observed.

The dumbbell-shaped crystals vary from 0.005 to 0.02 mm. in diameter. Under the polarizing microscope brush polarizations, similar to those of starch grains, are observed, which suggest that the crystalline structure is not completely formed. The orthorhombic hemimorphic crystals in the urine varied from 0.2 to 0.04 mm. in their largest dimension.

Specimens of urine containing dumbbell-shaped crystals yielded relatively large amounts of the acetyl derivative of sulfathiazole. The crystal structure of acetylated sulfathiazole is shown in Figure 3. These crystals were orthorhombic in structure and consisted of tabular and prismatic forms. The tabular forms were diamond-shaped, the longest diagonal dimension being from 0.01 to 0.05 mm. and the shortest from 0.005 to 0.03 mm. The thickness of the tabular form was approximately one-fifth of the shorter diagonal dimension.

In the prismatic forms the cross-sectional dimensions were approximately the same as those of the tabular forms. The height, however, was approximately two and a half times the shorter diagonal dimension of the cross-section.

Crystals of acetylsulfathiazole prepared by acetylating sulfathiazole with acetic anhydride were the same as those isolated from the urine, excepting that they were approximately two and a half times larger.

Sulfathiazole crystals were suspended in a solution of 0.9% sodium chloride and in normal acid urine. In the salt solution, the crystals appeared as flat pseudohexagonal plates somewhat resembling mica in structure. The dimensions of these crystals ranged from dust particles to a length of 0.3 mm. in the longest axis. Sulfathiazole crystals suspended in urine changed their shape to rectangular tablets. This change in configuration suggests that the crystalline structure of the compound may be polymorphous.

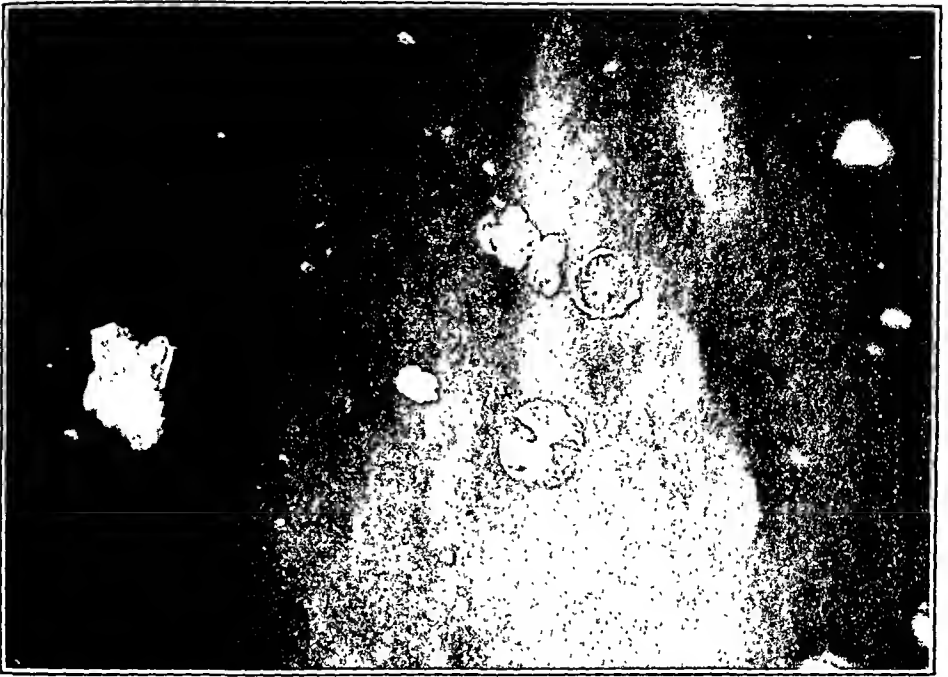


FIG. 2.—Dumb-bell shaped crystal in urine of patients receiving sulfathiazole.

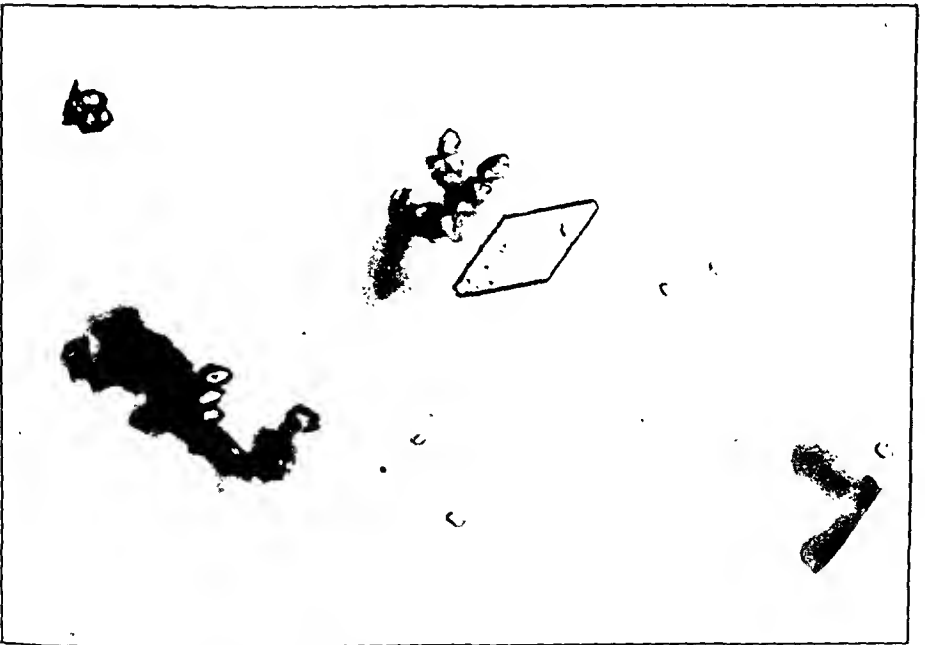


FIG. 3.—Diamond shaped crystal of acetylsulfathiazole.



**Recovery and Isolation of Acetylsulfathiazole From the Urines of Individuals Receiving Sulfathiazole.** Sediment from the urines of individuals receiving sulfathiazole was separated by centrifugation, pooled and repeatedly washed in water. This pooled, dried, crystalline sediment was heated with 20 cc. of a 1 to 1 mixture of acetone and water, and filtered. The residue on the Fisher-Jones melting point apparatus\* melted at 271° to 274° F. The behavior of the material was characteristic; it became hazy before melting and upon melting decomposed, forming a dark brown oil. Under the same conditions the synthetic product, obtained from the acetylation of 2-sulfanilamidothiazole with acetic anhydride, behaved similarly and melted at 272° to 275° F. The melting point of the synthetic acetyl derivative was unaltered by mixing with the product from urine, and the two materials were therefore regarded as identical.

**Summary.** Applying methods for the analysis of sulfanilamide in whole blood to the measurement of sulfathiazole, we have found that recovery of sulfathiazole in whole blood averages approximately 86% of the theoretical. This diminution in the recovery was shown to occur during protein precipitation. Employing serum instead of whole blood, loss of sulfathiazole is considerably less, averaging only about 3%. For this reason we feel that analysis for sulfathiazole should be made in serum instead of whole blood. A procedure for analysis in serum is suggested in which an arbitrary correction for the loss is made in the final calculation.

Since both sulfathiazole and its acetyl derivative are about twice as soluble in urine of pH 7.6 as in urine of pH 5.6 it may be inferred that when crystalline concentrations owing to sulfathiazole therapy threaten, an effort should be made to keep the urine alkaline and to secure a large urinary volume.

We wish to express our appreciation to Dr. Ralph A. Connor and Messrs. A. W. Postel and W. E. Haesler, Jr., for their aid, and to thank E. R. Squibb & Sons and the Maltbie Chemical Company for supplying us with adequate samples of the compounds.

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\* The Fisher-Jones apparatus was used because of the small amount of material required and the desirability of watching the melting under magnification. These melting points are higher than the values (256° to 257°), presumably determined in a capillary tube, which were reported by Fossbinder and Walter.<sup>2</sup> Considering the differences in the apparatus, the high melting point, and the decomposition upon melting, the discrepancy is not surprising. The characteristic behavior of the materials noted above makes this method especially convincing in confirming the identity of the products.

## OBJECTIVE ESOPHAGEAL CHANGES DUE TO PSYCHIC FACTORS.

### AN ESOPHAGOSCOPIC STUDY WITH REPORT OF 13 CASES.

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THE purpose of this paper is to show that the esophagus undergoes definite changes in response to emotional upsets. These changes can be observed with the esophagoscope, and the relationship between cause and effect positively established. As far as I am aware this has not previously been done.

The patients used in this study represent a cross-section of society from the wealthy to those on relief. Each sought treatment for symptoms that were ascribed to one or more of the organic systems. None of them came to us directly. All were referred, some because of complaints pointing to the esophagus, and others solely because of our interest in making this study.

Our investigative procedure consisted of the usual history and physical examination, essential laboratory tests, and necessary consultations. A detailed social, economic, and emotional history was obtained, recording the patient's worries, fears, apprehensions, difficulties and failures, as well as his hopes, pleasures, and aspirations.

An esophagoscopic examination was made in all cases, using local anesthesia, and noting the presence or absence of esophageal spasm and the size of the lumen. While the esophagoscope was in place, and direct observation possible, the patient was asked to imagine himself in situations which we proposed. These were selected with the aim of bringing forth desirable or undesirable sensations, feelings of security or insecurity. With each proposal or suggestion we noted whether any alteration occurred in the esophagus.

Although some form of fear or sense of inadequacy was a common feature in all these cases, for ease of presentation we have decided to arrange them in groups depending upon whether the difficulties were brought about by marital, social, occupational, or financial insecurity.

GROUP 1.—A twice-married woman, aged 33, an alcoholic, was referred for diagnostic esophagoscopy, because she had been vomiting and expectorating blood, and the possibility of an esophageal varix had arisen.

Except for a traumatically perforated nasal septum with ulceration and markedly dilated nasal vessels, the physical examination was essentially negative.

On the surface she was a mean, cruel, bitter patient. But one could sense that underneath this unpleasant exterior was a sensitive, bewildered person, who did not know where to turn for assistance. She was one of those who acted first and thought afterwards, thereby getting into difficul-

ties and, as a consequence, having to undergo detrimental emotional disturbances. Then instead of adjusting herself to the new situation or extricating herself from it, she expected others to pay for her mistakes, and vented her unhappiness upon any one who was at hand. To fully appreciate the significance of the esophagoscopy findings in her case one must know something more about her personal life and all incidents that might have initiated emotional conflicts.

Coming from a family that believed in the permanency of marriage, she was estranged from her parents by divorcing her first husband, and thereby lost the custody of her boy. Remarriage led to further controversy with her family.

In her second husband she thought she had "a reliable, industrious, kindly, intelligent, well-educated man," but he turned out to be an excessive periodic drinker, who spent his entire pay check for liquor, drove his automobile while intoxicated, and was arrested for this offense on several occasions. And added to this he boasted of his unfaithfulness. At this point of the history she volunteered that she "could go back to her first husband who wanted to remarry her," but this was said so unconvincingly that it appeared she might like to, but could not. They were badly in debt, but she emphasized that she had no desire nor intention of using her previously accumulated resources to meet her financial obligations.

*Esophagoscopy Examination.* There was no evidence of esophageal varices. But the entire esophagus was spastic and the lumen narrowed to one-half normal size.

While the esophagoscope was in place, she was asked how she "would feel if she had sufficient funds to meet all her obligations." This question brought forth no relaxation of the spasm or alteration in the size of the lumen. The proposal of a vacation elicited a sluggish but only slight relaxation.

The possibility that she might never see her boy again caused instantaneous and complete spasm with absolute closure of the lumen. Whereas, the suggestion that she might have her boy permanently with her brought forth a prompt relaxation of the spasm and a return of the lumen to full normal size, twice as large as was noted at the beginning of the examination.

Then told to imagine how she would feel if suddenly informed that her boy was dead, the esophagus clamped down with lightning speed, the lumen was obliterated, and the muscle quivered. These findings remained several minutes and they were still present when the next question was commenced.

"How would you feel if you got news that your present husband was killed in an automobile accident?" Therewith, the spasm immediately disappeared and the lumen opened widely. At the completion of the esophagoscopy she proffered: "You might as well know. It wouldn't make any difference to me, one way or another, if something happened to my husband."

It will be noted on review of this case that imaginary situations of a personally dreadful or undesired nature led to instantaneous spasm and closure of the esophagus. Thoughts of a pleasant or hoped-for variety caused prompt relaxation and proper widening of the lumen. Problems that were relatively unimportant in her scheme of life elicited correspondingly unimportant changes in the esophagus.

Her daily life presented enough emotional disturbance to account for the spasm and narrowing that were encountered even before the questions were asked.

GROUP 2.—The next 2 cases with esophageal complaints were financially independent bachelors, one aged 59, the other 63. Both were railway men regarded as successes in their respective fields, executive and train dis-

patcher. Overly serious and tense in all that they did, neither knew how to relax, and they got very little fun out of life.

The dispatcher continually dreaded the thought that ultimately he might make a mistake in his work and be responsible for a train wreck. The executive, whose duties called for numerous court appearances and exasperating cross-examinations by staffs of technical lawyers, never got used to testifying and abhorred it.

His medical complaint was pain along the left side of the cervical esophagus. The esophagoscopy examination revealed tremendous spasm of the inferior constrictor of the pharynx at the entrance to the esophagus. Proximal to this there was redness of the mucous membrane from stasis and subsequent infection. In addition, the entire thoracic esophagus was spastic and the lumen narrower than usual.

When the patient was asked to imagine how he would feel if he "could take a long vacation, and get away from both the monotonous routine and the disturbing court sessions," the spasm relaxed and the lumen became wider.

The proposal that he "continue to work under increased irritations and be subject to even more frequent court appearances" brought forth a spasm of the entire esophagus and closure of the lumen. This relaxation and spasm could be elicited consistently and repeatedly in response to desirable and undesirable proposals.

The other patient had symptoms of partial obstruction of the esophagus, restricting his diet to semiliquids. He was sent to us with a tentative diagnosis of hernia of the diaphragm through the esophageal hiatus and secondary pressure upon the lower esophagus.

The esophagoscopy findings were quite similar to those in the previous case, namely, spasm of the entire tube and narrowing of the lumen to one-third normal size. The spasm was particularly marked at the upper and lower sphincters.

When it was suggested that due to an error on his part he might be responsible for a serious train wreck, the spasm increased and the lumen narrowed still further. The proposal that he take a long vacation brought forth relaxation of the spasm and increase in the caliber of the lumen.

After this examination, when the character of the esophageal disturbance had been explained to him, he retired from his tension-producing occupation, bought a chicken ranch, and had no further trouble in swallowing and retaining a regular diet.

These 2 cases are examples of the esophageal spasms that occur in overly serious, conscientious people who lead, tense, straining apprehensive lives without proper intervals of relaxation and recreation. Long continuance of such an unhealthy routine could well enough keep the esophagus in a more or less constant state of spasm.

On the basis of the predominance of the spasm at the upper end in one of the patients and at the lower end in the other, I am inclined to believe that the former would ultimately have developed a cervical esophageal diverticulum, and the latter a cardiospasm with attendant dilatation of the lower esophagus.

GROUP 3.—In contrast to the financial status of the 2 previous patients, those in the present group must be classified as social and economic failures, haunted by the fears and uncertainties that attend such insecurity. For their livelihood they had to depend upon government relief, and hence, whenever curtailment of relief threatened, they were stricken with terror, apprehension, and spasm.

Since the problem is an economic one, no amelioration of symptoms should be expected from the use of atropine, tincture of belladonna, sedatives, or other drugs. Improvement and ultimate recovery are to be had only after

the patient has been shown a satisfactory way out of the situation and assisted in finding a new means of livelihood.

A woman, aged 33, recipient of a widowed-mother's pension, was informed that within a few months her daughter would have reached the age where no further state assistance could be allowed. Shortly thereafter her illness began, and she reported to the clinic complaining of "the sensation of a lump in the throat, difficulty in swallowing, and nausea."

Despite the morphine, atropine, and sedatives that were routinely given preliminary to the esophagosopic examination, we encountered a firmly resistant spasm of the inferior constrictor of the pharynx at the entrance to the esophagus. The balance of the esophagus was also spastic and thickened, and the lumen reduced one-half.

This spasm increased at once when the patient was asked to imagine how she would feel if, in addition to the discontinuance of the pension, her daughter should get married immediately and lend no financial assistance. On the other hand, the suggestion that she might get a son-in-law who would delight in providing the patient with all the necessities and a few of the luxuries of life initiated an immediate esophageal relaxation.

The next patient was a sullen, frustrated, unmarried Greek laborer of 52, a relief recipient, whose complaints were "pains in the chest and cramps in the bowels." He became ill at a time when relief rolls were being reduced and publicity had been given to the fact that the sick would not be stricken from the list. The man had lost all ambition, and his mental and physical responses had become outstandingly sluggish.

Endoscopic examination showed uniform spasm of the entire esophagus. The spasm was aggravated when it was suggested that he might be denied government aid. But, when asked to imagine how he would feel if located in a mountain camp enjoying the fresh mountain air and the smell of the pines, with a cook to supply an abundance of well-prepared food, and not a thing to worry about, there was a lessening of the spasm and a widening of the lumen.

Told to imagine how he would feel if he could get a job paying \$500 a month, there was no improvement in the spasm. Apparently he was not interested in anything for which he had to work, or, his imagination was not developed to the point where he could conceive of \$500 a month. In order to get an esophageal response I believe it is necessary for the proposed situation to be such that the patient can imagine the possibility of its actually happening.

In the previous cases the esophageal spasms and relaxations occurred immediately after the proper suggestion, but in this patient there was a 45-second delay between suggestion and reaction. It is conceivable that, with his slowed cerebration, each new thought had to await its turn before reaching the consciousness of the preoccupied brain.

GROUP 4.—There were 2 married men and a married woman in this group, aged 27, 31, and 30 respectively. All 3 were gainfully employed but just barely making ends meet, and, before 1 month was over they had to begin worrying about the oncoming month. They had no lack of imagination, but, on the contrary, set their goals so high that they were unequipped to attain them.

They were selfish, opinionated, and aggressive, as well as easily frightened and discouraged. All 3 attributed their difficulties to marriage, because previously they had had ample incomes and freedom from worry and family responsibility.

The woman's symptoms were poor appetite, frequent headaches, chilly sensations, diarrhea, insomnia, nervousness, dizziness, and pain over the precordia immediately after eating. There was also right upper quadrant pain with a feeling of suction whenever she stooped.



She was referred to us for this study after 3 years of treatment in the neurologic, gynecologic, gastro-enterologic, and otorhinolaryngologic clinics had afforded no relief of symptoms.

Endoscopic examination revealed a uniform spasm of the entire esophagus and a reduction of the lumen to one-third normal size. In addition, there was a small, rapid, continuous, irregular, intermittent, superimposed minor spasm, muscular contraction, or quivering. This looked like what one would expect to see if the heart were exposed during auricular fibrillation; and it also reminded one of the frequency of action of a telegrapher's key during the sending of a message. Nevertheless, this patient's heart action was not disturbed or abnormal in any respect.

I think there is a possibility that these secondary superimposed spasms may be a manifestation of a continuous stream of fresh emotional disturbances engrafting themselves upon the already well-established ones which had caused the major spasm. All the patients in this group had such superimposed spasms.

This patient's esophageal responses to suggestion were similar to those already reported. The major spasm became less marked following pleasant proposals, but showed additional tightening with anxiety situations. The secondary or superimposed spasms ceased when the major spasm relaxed; but they were inconsistent thereafter, sometimes returning with the return of the major spasm, and at other times failing to reappear.

The second patient in this group was referred with the complaints of nausea, vomiting, inability to swallow, and substernal pain. His esophageal spasm was so marked that it was only with the greatest difficulty that the esophagoscope could be introduced. The spasm extended throughout the entire length of the organ, and the grip of the esophageal muscles upon the instrument was so firm that considerable strength was needed in order to withdraw the esophagoscope even a few inches.

Despite this original degree of spasm, the esophagus relaxed fully and instantaneously, and the lumen opened widely when we proposed finding a job for the man and his wife that would be sufficiently remunerative to permit an assured monthly income without worry. The instrument could then be moved up or down with the greatest facility.

A picture of desperate poverty was painted, and the spasm returned. Alternating suggestions of security and insecurity caused alternating relaxation and spasm.

The next patient had also been treated in several departments of the clinic before being transferred for this esophageal study. His symptoms were dizziness, weakness, numbness of the hands, a sensation of fainting, and abdominal pains with nausea.

Esophagoscopic examination showed diffuse uniform spasm of the entire esophagus and reduction of the lumen to one-half normal size. When concrete suggestions of a better job and greater security were presented, the spasm immediately diminished and the lumen widened. When asked to imagine how he would like to have his mother-in-law come to live with him, attempt to regulate his life, and increase his household expenses, the spasm became aggravated and the lumen narrowed to one-fourth normal size.

GROUP 5.—Under this classification come 3 women and a man; 2 were married, 2 single. Their ages ranged from 39 to 64; and in each case there were very definite esophageal symptoms. All had more than a fair measure of financial security, but life had become unbearably monotonous with no prospects of its changing. They had a sense of encirclement, imprisonment, and frustration.

The 4 cases were so much alike that, to avoid repetition, a detailed account will be given in but 1. He was a serious, quiet, unmarried man of 39, the owner of an automobile repair shop, who was doing well in his business

and had an adequate savings account. His education was limited to grammar school. His brothers and sisters had all married and established homes of their own, leaving the aged, deaf mother with him. There was almost no conversation in his life. He ate alone and worked alone. He had no friends, no recreation, and no diversions. Every day was the same as the preceding one.

He was referred to us because of nausea, vomiting, and difficulty in swallowing. Endoscopic examination showed a diffuse uniform spasm of the entire esophagus with narrowing of the lumen. There were no superimposed minor contractions. When he was asked to imagine how he would feel if he could escape from his environment, take a vacation, and get some pleasure out of life, the esophageal spasm relaxed immediately and the lumen widened. The reminder that he might have to continue living as he had been doing caused the spasm to return and the lumen to narrow. A rationalized, balanced scheme of living was arranged for this man, and since that time he has been eating a regular diet without recurrence of symptoms.

*An Exception.* For 4 years a married woman, aged 31, the mother of 3 children, had complained of blurring vision, spells of dizziness, nervousness, abnormal fatigue, headaches, pain in the right lower quadrant, bloating and abdominal cramps; and during that time she was treated without relief, repeatedly visiting the departments of ophthalmology, internal medicine, proctology, and gastro-enterology. And a few months before we saw her, she had acquired the additional symptoms of difficulty in swallowing, vomiting, and pain with a sense of fullness under the upper end of the sternum.

Her emotional history revealed that she was worried, apprehensive, and insecure financially. She feared that she would not be able to properly clothe and adequately educate her children, and was quite disturbed because of her inability to take a much needed vacation from the monotonous household duties.

Esophagosopic examination showed a constant, uniform spasm of the entire esophagus and narrowing of the lumen to one-third normal size. Engrafted upon this were the waves of a superimposed intermittent minor spasm.

But suggestions, proposals, and exhortations failed to alter the spasm. There was no relaxation at any time. The possibility of a greater income, a long pleasant vacation, desirable educational facilities, and a new home elicited no response. Unfavorable situations were likewise ineffective in changing the picture.

Had this been the first patient in our study, or had we encountered several of this type at the very start, we would undoubtedly have been led astray in evaluating the influence of suggestions, thoughts, and emotions upon the esophagus. But this case, coming as it did after we had already been thoroughly convinced through our previous studies that the esophagus would respond if the proper subjects had been touched upon, was not hard to understand.

We challenged her story and accused her of having withheld vital information relative to her difficulties. On this point we were very firm, emphasizing that she could not be helped unless she presented her complete problem. This she indicated she would do if the instrument were removed.

Her story confirmed our suspicions. Her overwhelming emotions were regret and remorse. These arose from an irreparable past deed which incited and maintained the uncertainty and fear that as a result she might have to face unpleasant consequences in the future.

Motherless at the age of 5, this girl at 20, while unmarried, became pregnant and had to continue living in a small town where every one knew and saw her. She gave birth to her baby 2 months before the father of

the child could be found and compelled to marry her. The patient's father considered the affair a family disgrace, immediately disowned her, and forced her to move to another city. He died some years after without permitting a reconciliation.

Dreadfully lonesome for an occasional visit with her family, this youngster was denied that privilege by the dictate of her father and the fear of town gossip. There was the added hazard that her son, now grown older, might hear of the incident and learn to hate her. In view of this history it can be seen that we did not ask the proper questions during the esophagosopic examination and hence failed to get either relaxation or altered spasm.

**Summary and Discussion.** Twelve cases are reported in which spasm of the entire esophagus was noted and studied by means of the esophagoscope, for the first time as far as I am aware. It was seen that the spasm could be aggravated or relieved, depending upon the type of emotions which were aroused.

All of the patients had a sense of inadequacy, insecurity, or impending trouble. The type of insecurity varied, being either maternal, religious, occupational, social, financial, or marital.

One case is reported in which the spasm was neither relieved nor aggravated by suggestion. This patient later admitted that she had given a false emotional history, but we suspected this at the time of the esophagosopic examination.

The esophageal reaction and alteration in the spasm is in direct relationship to the personal vitalness of the problem; and, conversely, situations in which the patient has no vital interest are incapable of eliciting an esophageal reflex.

In addition to causing uniform spasm of the esophagus, we believe that disturbing emotional influences are also underlying factors in the production of certain esophageal strictures, cardio-spasm, and certain so-called idiopathic pressure diverticula of the esophagus.

Antispasmodics, atropine, tincture of belladonna, and sedatives cannot, in themselves, be expected to afford relief in these patients whose esophageal spasm is brought about by financial insecurity and other serious personal inadequacies. Medicinal therapy alone merely delays proper treatment and allows the condition to progress to an advanced stage.

It goes without saying that all cases with even the slightest esophageal symptoms should be examined by means of the esophagoscope to ascertain the cause of the disorder, and if the trouble is shown to be on an emotional basis the patient should be placed in the hands of a psychiatrist for emotional reëducation, change of mental outlook, and social adjustment.

But it must be clearly understood that no case is to be classified as an emotionally-spastic esophagus and so treated without first positively establishing the diagnosis by esophagosopic examination, because identical symptoms can occur from stricture, ulcer, carcinoma, and esophageal foreign bodies.

Although the scope of this paper is limited to the esophagus, there is no reason to presume that these spastic emotional effects should be confined solely to this single organ. They undoubtedly occur in all the hollow viscera, including the various ducts, and account for a multitudinous array of symptoms. We have seen 3 cases, at bronchoscopic examination, in which the bronchus alternately widened and tightened in response to favorable and unfavorable suggestions. The significance of these observations in relation to asthma can be readily appreciated.

**Conclusions.** 1. By means of the esophagoscope we were able to show objectively that disturbing thoughts and emotions produce esophageal spasm.

2. This spasm can be increased and the esophageal lumen narrowed or closed by suggestions that call forth destructive emotions, such as grief, anger, anxiety, apprehension, fear, and spiritual imprisonment.

3. The spasm relaxes and the lumen widens immediately when proposals are made eliciting such emotions as happiness, elation, enthusiasm, contentment, and security.

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## ROENTGEN RAY THERAPY IN THE TREATMENT OF HERPES ZOSTER.

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HERPES zoster is an extremely painful disease. It is usually not dangerous except when there is involvement of the eye. A variety of treatments has been used, with questionable relief of symptoms; therefore we are presenting this paper on the use of Roentgen ray therapy because of our successful results.

Herpes zoster is a disease due to an irritation of the sensory extramedullary ganglia of the cranial nerves or of the posterior root ganglia of the spinal nerves, which manifests itself by groups of

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vesicles on the skin or mucous membranes along the course of the nerve or nerves involved. The theories of etiology of this disease are numerous.<sup>3,5,9,10,13a,b,15,16</sup> The most widely held today is that it is an inflammatory or irritative process in the ganglion itself from a specific virus or a non-specific invasion such as cancer, leukemia, lues, or an irritation from trauma or drugs such as arsenic. There is some evidence of a close relationship to other virus diseases such as chickenpox.<sup>4,8,14,17</sup> There is confusion in some of these cases reported as herpes zoster because there is no clear differentiation between this and herpes simplex.<sup>4,5,8,10,13a,b,14,17</sup> We will not go into a discussion of the differential diagnosis in this paper. Much work is still to be done, and we hope that with the advancement of knowledge of virus diseases, we shall learn more about the etiology of herpes zoster.

The seriousness of herpes zoster depends not only on the intensity of the symptoms and extent of the vesicles but also on the age of the patient, its location and the unknown factor of individual resistance. The eruption may be preceded or accompanied by pain, burning, itching and tingling. The extent of the vesiculation does not bear a direct relationship to the intensity of these symptoms. The postherpetic syndrome of pain, itching, tingling, burning, and so on, is often the most troublesome part of the disease and may persist for many months.

The treatment has not been as satisfactory as the many different methods would suggest.<sup>1,2,4,6,7,11a,b</sup> It is a self-limited disease which varies greatly in intensity, extent, and severity of the lesions. These facts must be kept in mind when evaluating the effect of any therapy.

For the relief of this syndrome, many things have been tried with varying results: ointments, lotions, heat, administration of such substances as pituitrin,<sup>11a,b</sup> vaccines, arsenic, codeine, and salicylate.

Roentgen ray has been previously used by others, notably Pillsbury,<sup>12</sup> Pendergrast, Kechline,<sup>6</sup> Wood and Knox.\* By radiating the spinal ganglion, Kechline in his series of 66 cases showed a diminution of pain and no further development of the cutaneous lesions. His results were best in the early cases. Wood and Knox have had similar experience. Pillsbury used a more superficial therapy over the local lesions and spinal ganglia, and found less effect on the pain than on the eruption. Our findings more nearly parallel Kechline's work.

We also agree with Bailey<sup>1</sup> and Byrnes<sup>2</sup> who recommend that Roentgen ray therapy be used in the postherpetic neuralgias before the more drastic surgical procedures or alcohol injections are employed.

**Source of Material.** Our entire series of 123 cases of herpes zoster consists of material seen in the medical and dermatological clinics

\* F. C. Wood and Leila Knox have kindly supplied us with the data on cases referred to them for treatment by one of us.

of New York Hospital and a few from private practice. There were 72 who received Roentgen ray therapy and 51 who did not. The type of treatment administered was unrelated to the severity of the disease. It depended entirely upon the physician into whose care the patient came. The results of the treatment of the two groups therefore offer a reasonable evaluation of the effectiveness of Roentgen ray therapy. Of the 51 cases in the control group, 14 received injections of pituitrin, others were given sedatives and salves or were merely observed to determine the duration and severity of the disease. There were no recurrent cases in our series.

We became interested in the treatment of herpes zoster because we saw a number of patients disabled by postherpetic pain.

**Age, Sex and Race.** Chart 1 shows the distribution according to age and sex of the control and treated cases.

CHART 1.—AGE AND SEX.

	Total.	10-20 years.	21-30 years.	31-40 years.	41-50 years.	51-60 years.	61-70 years.	71+ years.
Males . . .	48	2	3	6	4	9	13	11
Females . . .	75	2	6	8	16	27	11	5
Totals . . .	123	4	9	14	20	36	24	16

There were 48 (39%) males and 75 (61%) females. In Kechline's series 90% of the cases were males. In this series 4 (3%) were under 20 years of age, 43 (35%) were between 20 to 50 years and 76 (62%) were over 50 years. This is a much higher per cent of patients over 50 years than is found in the clinic group from which the majority of these patients were taken. Most of the reports in the literature fail to mention the age distribution. Kechline states his cases were 5 to 82 years of age. One of our patients was Japanese and the other 122 were of mixed origin of the white race.

CHART 2.—COMPOSITE CHART OF ALL THE CASES OVER A 6-YEAR PERIOD.

	Jan.	Feb.	Mar.	Apr.	May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.
No. in groups of 3 mos.	13	10	10	4	9	5	12	3	18	24	4	11
	33			18			33			39		

**Seasonal Distribution (Chart 2).** The highest individual incidences were in September and October, although on the whole there is very little difference in the groups of 3 months. This lack of seasonal variation corresponds to the observations of others.

**Location.** The skin lesions of the treated cases showed that the nerve roots were involved in essentially the same distribution as in the series of Kechline's patients: cranial 6, cervical 4, cervical and thoracic 4, thoracic 41, thoracic and lumbar 2, lumbar 15.

**Our Present Method of Treatment** is to give the patient 200 r daily or every other day, for 5 or 6 treatments, using 200 K.V. through 1 mm. of copper and 1 mm. of aluminum filter at 50 cm. distance in a 6 by 15 portal directly over the spinal root ganglia of the

nerves involved. In some cases treated, a lower total dosage was used because of factors beyond our control.

CHART 3.—RESULTS OF TREATMENT TABULATED ACCORDING TO DURATION OF DISEASE BEFORE FIRST TREATMENT, AND THE AMOUNT OF TREATMENT.

Total Roentgen ray therapy used (expressed in r).	Result.	No. days duration of disease before treatment.				
		1-3 days.	4-7 days.	8-14 days.	15-28 days.	29+ days.
1 to 400 . . . . .	5 cured	1	3	..	..	1
	0 improved	..	..	..	..	..
	0 failure	..	..	..	..	..
401 to 800 . . . . .	16 cured	7	5	3	1	..
	0 improved	..	..	..	..	..
	2 failures	1	..	..	..	1
801 to 1200 . . . . .	21 cured	4	8	3	1	5
	1 improved	1	..	..	..	..
	6 failures	..	..	1	2	3
1201 to 2400 . . . . .	14 cured	5	6	2	..	1
	3 improved	..	1	1	..	1
	4 failures	2	..	1	..	1
Total No. of patients treated . . . . .		21	23	11	4	13
		56 cured				
		4 improved				
		12 failures				

The onset of vesiculation is considered to be the onset of the disease.

Result of Treatment is shown in Chart 3. A study of this chart shows that the largest number of the patients in this series were treated within the first week of the disease. Twenty-one patients had had their symptoms for 1 to 3 days, 23 for 4 to 7 days, 11 for 8 to 14 days, 4 for 15 to 28 days and the remaining 13 had had the herpetic syndrome for over a month. Of this last group, 5 (38%) were failures and 1 was not completely cured.

CHART 4.—TOTAL DURATION BEFORE CURE.

	Control cases.		Treated.	
	Number.	%.	Number.	%.
1 to 3 days . . . . .	0	0	1	2
4 to 7 days . . . . .	2	4	7	12
8 to 14 days . . . . .	8	16	26	46
15 to 28 days . . . . .	8	16	13	23
29 to 60 days . . . . .	18	35	5	9
2 to 4 months . . . . .	11	21	2	4
4+ months . . . . .	4	8	2	4

NOTE.—Table does not include the failures or the incomplete group.

In Chart 4 is analyzed the percentage of cures in relation to the time required. In the cases treated with Roentgen ray 46% were cured within 8 to 14 days, whereas only 16% of the control group was relieved within this period. Furthermore, it required 28 to 60 days to cure 35% in this latter group.

In the Roentgen ray series there were 9 cases who required over 1 month for cure. Of these, only 1 was seen within 30 days of the onset of the disease. This patient received his first treatment on the third day and was given 1800 r. He was relieved of his pain

after 1 month. The other 8 cases were not seen for 1 to 8 months after the onset of symptoms.

CHART 5.—RELATION OF THE TIME OF TREATMENT TO SUCCESS ACHIEVED.

Duration (in days) of disease before treatment.	Cases treated.		Cases cured.	
	Number.	%.	Number.	%.
1 to 7 . . . . .	44	61	39	89
8 to 14 . . . . .	11	15	8	72
15 to 28 . . . . .	4	6	2	50
29+ . . . . .	13	18	7	54

Thirty-nine of the 44 cases (89%) treated in the first 7 days of the disease were completely relieved. Two of the remaining 5 were improved and the other 3 received no benefit from the treatment. Of the 11 treated between the eighth and fourteenth day, there were 8 completely relieved (72%), 2 were partially benefited and 1 was a failure. Of the 4 treated between the fifteenth and twenty-eighth day, 2 (50%) were cured and 2 were failures. Of the 13 treated after the twenty-ninth day, 7 (54%) were cured, 1 was partially benefited, and 5 were completely unrelieved. This analysis shows very conclusively the importance of treating cases of herpes zoster promptly, inasmuch as the cures in the first 7 days were 89%, as compared with only 50% after 14 days.

CHART 6.—FAILURES (12 CASES).

Sex.		Duration before treatment.	Total Roentgen ray therapy (r).	Year treated.	Age in years.			
Male.	Female.				41-50.	51-60.	61-70.	71+
GW		5 mos.	900	1935	..	..	*	
	BD	1 yr.	960	1935	..	*		
	LD	1 day	800	1936	..	*		
	DG	1 mo.	600	1936	..	..		*
FD		3 mos.	1600	1937	..	..	..	*
HS		1 mo.	900	1937	..	*		
EM		7 mos.	1050	1937	..	..	*	
	MH	8-14 days	2400	1937	*			
	MS	Pain 2 wks. before erup.; erup. 3 wks.	1200	1937	..	..	*	
DL		3 days	1600	1939	..	..	*	
	FW	2 wks.	2000	1939	..	..	*	
EC		3 days	1600	1939	..	..	..	*
6	6	2 days	600	1935	1	3	5	3
		to	to	to				
		1 yr.	2400	1939				

There were 6 men and 6 women in the failure group. Chart 4 shows a higher percentage of men when compared to the total number in the series. Eleven of the 12 cases (92%) were in the group over 50 years of age which is higher than the same age distribution (77%) for the entire group. From this it is found that the older group shows a lower percentage of cures than the younger.

The only 2 cases treated before the fourth day of the disease who failed to respond to Roentgen ray therapy have presented interesting problems. They both received a total of less than 2000 r. The first, a man of 74, has been in the hospital for more than



6 months because of his pain and has failed to respond to any of the many therapeutic measures employed. The other, a woman of 60, was placed in the early group because she was treated within 18 hours after the appearance of the vesicles. However, she had complained of severe pain and itching for the previous 2 weeks. The eruption was spreading extensively, but after the second exposure to Roentgen ray the itching ceased and there was no further spread of the vesicles. However, the pain was not alleviated in the least by Roentgen ray therapy, nor by subsequent alcohol injection. She was unable to come in regularly and her total dosage was not as great as we should have preferred. After the end of 3 years she still has the constant pain in the distribution of the original lesions.

**Discussion.** We have already shown that the success of this treatment is directly dependent on the duration of the disease. We have found repeatedly that treatment has been delayed because the physician has considered the extent of the cutaneous lesion at the onset too insignificant to warrant Roentgen ray treatment. Then, because of persistent pain, he has referred the patient for treatment after the optimal date for relief has passed.

We have observed that the symptoms may be exaggerated after the first treatment. It is therefore important to warn patients of this reaction and advise them that improvement will follow subsequent treatments.

There is a tendency for patients to desist from Roentgen therapy after a few treatments because of the relief from pain and because the local lesions do not show further spread. It is important to insist on the full course. Although some may respond to smaller doses, we have found it wise to give the total of 1000 to 1200 r because, after a brief interval in an occasional one of our insufficiently treated cases, there has been a recurrence of the pain and parathesias which were relieved by further treatment.

**Conclusion.** From this study of 72 cases of herpes zoster we believe that Roentgen therapy is an ideal agent for the relief of herpetic syndrome and that better results will ensue if adequate treatment is started early.

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## BLOOD STUDIES IN MALARIA.

THE GENESIS OF BLOOD CELLS IN RELATION TO TREATMENT  
WITH QUININE.

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BLOOD studies in malaria in relation to treatment were limited to those concerned with the rate of production of hemoglobin and erythrocytes until investigations concerning the regeneration of blood in pernicious anemia after treatment with liver led to similar studies in malaria. Davidson and McCrie<sup>3</sup> found that the degree of reticulation in malaria was proportional to the degree of anemia and to the ability of the bone marrow to respond to it. Yang and Berglund<sup>20</sup> observed an increase of reticulocytes and eosinophils during the treatment of a case of tertian malaria with quinine bisulphate. Benhamou<sup>1</sup> obtained reticulocytoses as high as 19% in the course of the anemia due to malaria, but did not make clear the relationship to treatment. Eight days after treatment with quinine was started Farley<sup>4</sup> obtained reticulocytoses as high as 37% in monkeys (*Macaca mulatta*) infected with *Plasmodium knowlesi*. He also obtained persistent submaximal reticulocytoses in the instances in which treatment resulted in chronic infections with only a few parasites in circulation. He and Bromfield<sup>5</sup> found very little increase of the reticulocytes in experimental human infections, in spite of the anemia, but obtained counts in the natural human infections which ranged from 0.6% to 10.9%. They observed reticulocytoses consistently after treatment, and found that the intensity of response was dependent on the degree of anemia, and that the maximum reticulocytosis averaged 29% and occurred 6 to 10 days after treatment had been started. They concluded that an increased production of red cells followed the destruction of parasites, and was quite independent of the administration of hematinics. Menon, Krishnaswamy and Anamalai<sup>12</sup> found an average reticulocyte count of 1.06% in 10 cases of acute malaria and of 3.55% in 7 cases of chronic malaria. They obtained a rise in count following treatment with quinine. Pokrowski<sup>15</sup> reported a reticulocyte count of 1% in a case of tertian malaria, and of 0.2 to 10.6% in cases of chronic estivo-autumnal malaria. Studies of the bone marrow were made in the latter cases and the per cent of reticulated erythrocytes was found to vary between 0.8 and 3.7. Malamos<sup>10</sup> studied the blood of monkeys (*Macacus rhesus*) inoculated with malaria and obtained reticulocyte counts varying from 0.1% to

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3.5% in infections with *Plasmodium knowlesi*, and from 0.7% to 2% in infections with *Plasmodium cynomolgi*. In 2 cases of infection with *Plasmodium vivax* Kitchen<sup>7</sup> found an elevation of reticulocytes to 100,000 cells per mm.<sup>3</sup> on the fifteenth and twenty-second days of the infection, respectively, and continuance at that level until the fifty-fourth and fiftieth days.

It is obvious from these studies that, while regeneration of red cells is more or less active in malaria *per se*, it is definitely stimulated to greater activity incident to treatment and removal of the parasites from the blood. There are few reports, on the other hand, concerning the effects of the same factors upon the white cells.

Bunker<sup>2</sup> studied the blood of 10 paretics during paroxysms in the course of therapeutic infections with tertian malaria. In 9 of the cases he found that a decrease of the white count always occurred during the period of rising temperature and was followed by a leukocytosis 2 to 4 hours later in 77% of the paroxysms studied. He considered that the leukocytoses were analogous to the effects of intravenous injection of foreign protein. Ross and Thompson<sup>16</sup> observed leukopenias ranging from 300 to 2000 cells per mm.<sup>3</sup> during the paroxysms of malaria. The white counts increased coincident with subsidence of fever and disappearance of asexual forms of the parasites, following treatment with quinine. Counts of 20,000 to 30,000 were obtained, but not maintained, about 7 days after treatment was started. The authors believe that the high counts were related to the large amounts of quinine present in the system at the time.

The leukocytic picture following administration of quinine in malaria cannot be adequately evaluated without consideration of the effect of quinine upon the leukocytes of normal individuals. The benzene ring is a component of various substances which cause chemical agranulocytosis. Quinine contains that ring and is listed among the drugs which cause agranulocytosis in man. It has been blamed as the causative agent in various clinical conditions in which quinine was a part of the therapy and in which agranulocytosis developed during the course of treatment. In their handbook of hematology, Kracke and Garver<sup>8</sup> state that quinine has been "suspected" of causing suppression of the leukocytes in some instances. Groen and Gelderman<sup>6</sup> reported a case in which fever and the complaint of headache and pain in the neck, accompanied by progressive leukopenia, followed the administration of sodium salicylate and quinine. Four days before death the white count decreased to only 1444 cells per mm.<sup>3</sup> with 12% neutrophils, and necrotic angina ensued. Norris<sup>13</sup> reported the case of a patient who took quinine to control fever before coming under observation and to whom 20 gr. of pyramidon were given 2 days before the first blood count was made. The total white count was found to be only 150 cells per mm.<sup>3</sup> with a complete suppression of the granulocytes. Norris also

observed several cases of malaria in which death occurred during treatment with quinine after parasites had disappeared from the blood, and he suspected that the deaths were due to agranulocytosis caused by the quinine.

It is only in the case reported by Vitug, Chavez and Austria,<sup>19</sup> however, that a causal relationship of quinine to agranulocytosis seems definitely justified. The patient had been taking 1.2 gm. of quinine bisulphate daily. She developed a progressive leukopenia which by the seventh day of treatment had decreased to a level of only 700 cells per mm.<sup>3</sup> with 1% granulocytes. The quinine was discontinued and a blood transfusion was given. The white count returned to normal. After recovery, a second course of treatment with quinine was started in doses of 0.9 gm. daily. Four days later reductions of the granulocytes again occurred. The quinine was discontinued and the white count once more returned to normal.

Hematopoietic sensitization to quinine seems to be proven only in relation to the platelets. Peshkin and Miller<sup>14</sup> reported the case of an individual in whom an allergic status was established by injection of quinine and who developed thrombocytopenia, positive skin reaction and passive transfer reaction when subjected to a levorotatory group of chinchona compounds. They also cited a case reported by Maritschek and Markowitz<sup>11</sup> in whom 0.3 gm. of quinine produced severe thrombocytopenia with purpura and hemorrhages 15 years after the patient had suffered from quinine poisoning.

Reports based on experimental administration of quinine are few and contradictory. Vincent<sup>18</sup> found a diminution of the total leukocytes following injections of quinine in rabbits and guinea pigs with an immobilization of the white blood cells after large doses. In the human he observed a diminution of the white count 1 to 17 hours after quinine was taken by mouth. Lewetayer<sup>9</sup> concluded that subcutaneous injection of quinine chloride in the horse provoked an increase in the circulating neutrophils, but his figures are not significant. Roth<sup>17</sup> obtained lymphocytoses for several hours after administration of quinine in normal humans, but no significant effect was noted upon the granulocytes. The lymphocytoses, however, were succeeded by lymphopenias which were accompanied by an increase in the granulocytes. These observations were made during the first 24-hour period after administration of single doses of quinine. Roth also studied the effects of prolonged administration of quinine to dogs, and found that this resulted in a reduction of eosinophils and of lymphocytes and in an increase of granulocytes with death on the fifteenth day.

While these various reports indicate that both quinine itself and the treatment of malaria by the drug elicit definite modifications in the different strains of blood cells, they are for the most part limited to observations upon only one strain at a time, and are consequently uncorrelated. The studies to be reported were there-

fore undertaken in order to correlate counts of both the red and the white cells with treatment and with the progress of the malarial infections, so as to determine any interdependence which may exist between these factors.

This presentation is based on data obtained during a preliminary survey in 1935. Since it has been impossible to continue the work as planned and the data obtained are consistent in each case and represent a correlation not previously reported, it seems indicated to present it. The data are assembled from counts of the reticulocytes, erythrocytes and leukocytes made during the treatment of 4 patients<sup>2\*</sup> with estivo-autumnal malaria.

**Material and Methods.** The first erythrocyte count of each patient is taken from the routine hospital record made at the time of admission. The remainder of the counts were made as follows: The tip of the finger was punctured so that it bled without squeezing. The first 2 drops were discarded. Thomas pipettes were used for both the red and the white counts. The dilution for the white counts was 1 to 50, and for the red counts 1 to 400. The counts were made in duplicate on both sides of the counting chamber. When leukopenia was present, the white counts were repeated within 1 to 4 hours of each other, and an average of the two counts is used for the records. Two to 500 cells were included in the differential counts, which were made on specimen slide smears. Until the eighth day of treatment, only reticulocyte counts were made. After that, complete blood examinations were made daily.

The reticulocytes were counted in wet smears stained with brilliant cresyl blue. The per cent was obtained on the basis of the number met in a count of from 2000 to 5000 red cells. The number per mm.<sup>3</sup> was computed on the basis of the percentage of the total red cell count.

The 4 patients who served for these studies were sisters with coincident infections with estivo-autumnal malaria. Myrtis (Case 1) was admitted in a state of coma. The other 3 sisters were admitted 3 days later because they were found to have malarial parasites in the blood. All had been sleeping in the same room, which was inadequately screened. It is presumed that all 4 were infected with the same strain of parasites.

The treatment given during the periods of observation is indicated in the charts of experimental data. The diet was soft. The children were all undernourished and anemic; Myrtis and Mary (Cases 1 and 2) more so than the other 2. Any other relevant clinical material is given in the following brief case abstracts.

**Clinical Notes.** CASE 1.—(Charts 1 and 1A.) Myrtis L., aged 8 years, was admitted in coma. While under treatment the temperature was remittent and intermittent for 7 days. The maxima varied from 100° to 105° F.

CASE 2.—(Charts 2 and 2A.) Mary L., aged 11 years, history of chills and fever. The temperature was irregularly intermittent. The maximum was 102° F. It returned to normal 8 days after treatment was started.

CASE 3.—(Charts 3 and 3A.) Nellie L., aged 4 years, history of chills and fever. During the first 4 days of treatment the fever was remittent, reaching a maximum of 102° F. It became normal on the fifth day.

CASE 4.—(Charts 4 and 4A.) Elinor L., aged 7 years, history of chills and fever. The temperature was remittent around 100° F. during the first 4 days of treatment.

\* Dr. Claude McK. Burpee, Professor of Pediatrics, Georgia University School of Medicine, kindly permitted the study of these patients.

**Results.** The relationships brought out by the counts can best be observed by reference to the charts. A reticulocytosis followed the regression of the fever and the disappearance of the asexual forms of the parasites from the circulation. It was coincident with the appearance of numerous gametes. On the third day after treatment was begun the reticulocytes ranged from 0.1% to 3.5%, or about 4000 to 100,000  $\text{mm}^3$ . The number was definitely increased by the eighth day after treatment in all but Case 1. In that case the percentage was still only 0.1% on the sixth day after treatment was started but rose to 7% 5 days later, or 4 days after the temperature reached normal. The peak of the reticulocytosis occurred on an average 11 days after the start of treatment. The reticulocytes remained elevated at levels between 400,000 and 600,000 per  $\text{mm}^3$  for 7 to 9 days after the peak was attained. They then began to fall abruptly on an average of the nineteenth day from the start of treatment.

The erythrocytes were microcytic at the time of admission. They decreased progressively in number from the beginning of treatment until an average of 11 days thereafter, at which time they had fallen to their lowest levels. By that time the reticulocytes had increased to their peak. Numerous crescent bodies were present in the dry smears during the period of reticulocytosis, and were probably representative of ruptured erythrocytes. The total red count remained depressed to an average level of 2,500,000 per  $\text{mm}^3$  during the period at which the reticulocytes remained stationary at a peak. After the reticulocyte count began to decrease on about the nineteenth day from the beginning of treatment, the red counts progressively increased and normal-sized erythrocytes began to appear.

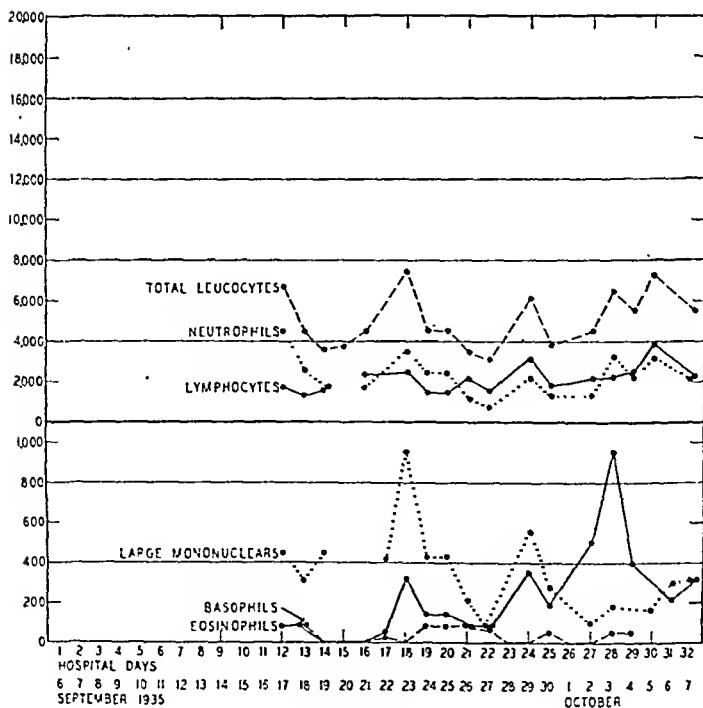
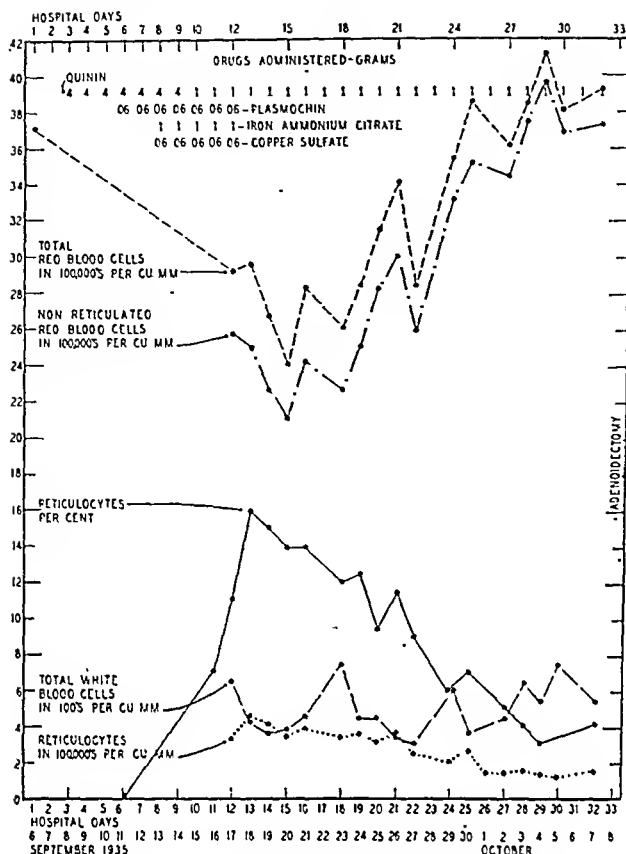
The leukocytes ranged from 7000 to 16,000 per  $\text{mm}^3$  until about the eleventh day of treatment. At about that time, which was the period of greatest increase in reticulocytes and greatest decrease in erythrocytes, the leukocytes began to decrease. The decrease was largely at the expense of the neutrophils and continued progressively throughout the period of reticulocytosis. The lowest levels usually occurred within a day preceding or following the time that the reticulocyte counts began to decrease to normal. From that time the neutrophils increased progressively, and this progressive increase was accompanied by a marked eosinophilia.

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#### LEGENDS FOR CHARTS 1 TO 4 AND CHARTS 1A TO 4A.

CHARTS 1 to 4.—(Cases 1 to 4.) Total red and white counts; percentage of reticulocytes; absolute number of reticulated and non-reticulated erythrocytes; treatment.

CHARTS 1A to 4A.—(Cases 1 to 4.) Total white counts and absolute number of the different white blood cells during the period of treatment.







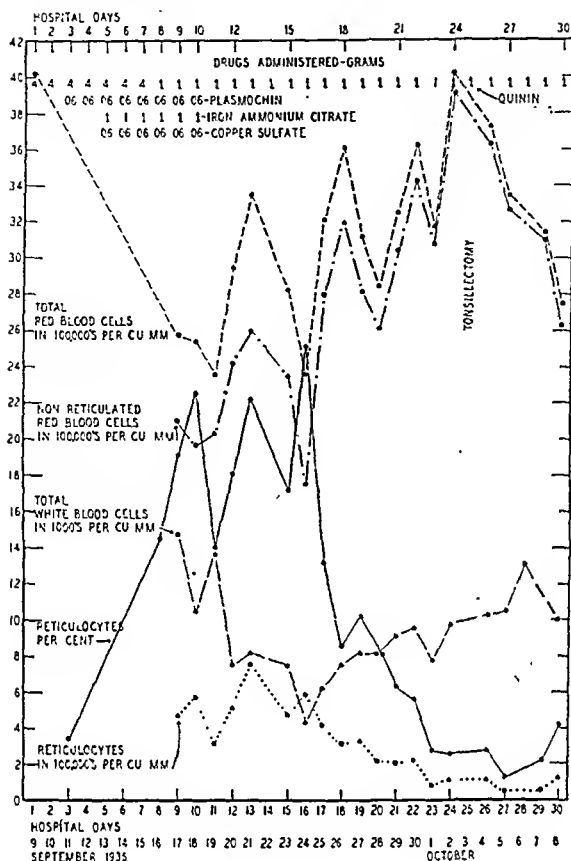


CHART 3.

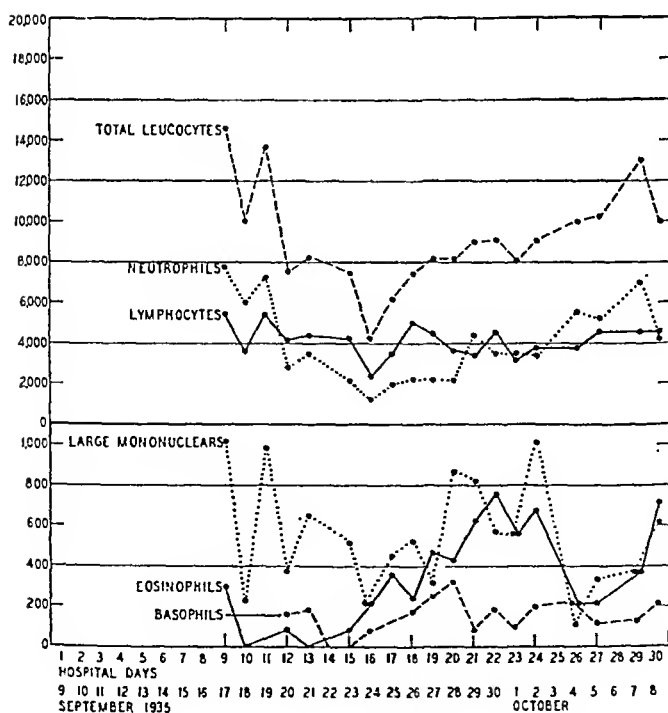
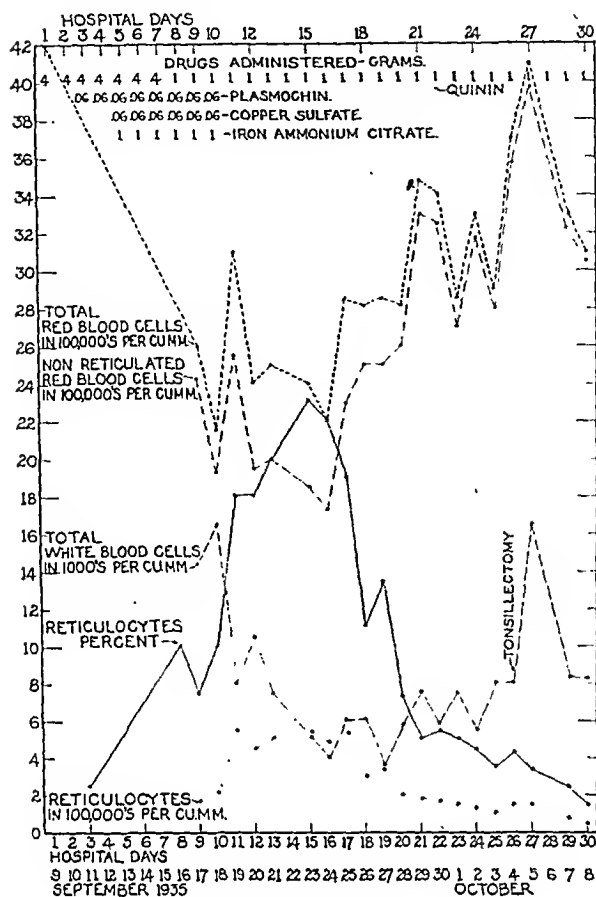
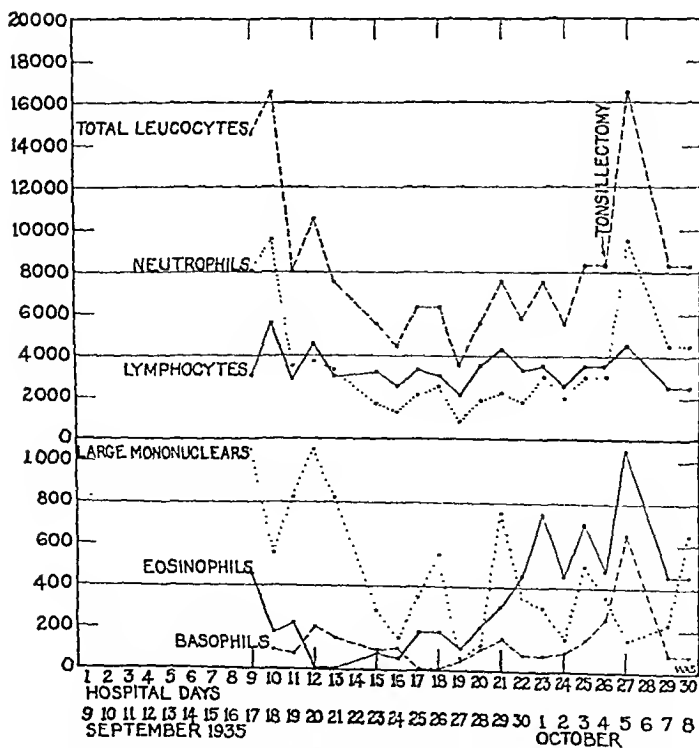


CHART 3A.



#### CHART 4.



The lymphocytes remained stationary throughout the periods of observation. In the 2 younger sisters (Cases 3 and 4) the counts were about 4000 per mm.<sup>3</sup>, and in the 2 older sisters (Cases 1 and 2) about 2000 mm.<sup>3</sup>. The differences in the minimal total white counts in the 4 cases at the periods of leukopenia are dependent mainly on the lymphocytic levels in each case.

Basophils were uniformly present during the period of observation. They varied from 40 to 400 per mm.<sup>3</sup>, and their presence in the smears in such numbers was most striking during the periods of leukopenia.

The number of large mononuclear cells varied from day to day without respect to the clinical status and followed no definite curve.

**Discussion.** Data obtained from other patients, both children and adults, admitted early in the course of malaria and in a state of good nutrition, indicate more rapid regeneration of the red cells after beginning treatment with quinine than occurred in these 4 cases, more rapid return of the erythrocytes to normal, and frequently leukocytoses subsequent to brief period of leukopenia. Since these are quantitative rather than qualitative differences from the findings in the patients reported here, it seems probable that the prolongation of the various stages in hematopoietic activity in these children is related to the degree of cachexia and is a reflection merely of a more sluggish marrow secondary to it. The prolongation itself has served to permit of enough observations at each stage of recovery to bring out the salient points of that stage.

Obviously in these cases, the regeneration of red cells, as indicated by the appearance of reticulocytes, followed the subsidence of fever and the disappearance of asexual forms of parasites, incident to treatment with quinine. That the regeneration was due to the quinine *per se* is unlikely. That it was due indirectly to the quinine, however, by virtue of the depressant effect of the drug upon the parasites and the consequent removal of toxic factors caused by the parasites, seems likely.

That the white count should decrease during the period of most active formation of reticulocytes, and again increase when reticulocytosis subsides, seems to be directly related to the genesis of blood cells and not due to quinine. This is particularly likely in view of the experiments of Roth with dogs, and in view of the fact that treatment with quinine was continued well past the period of leukopenia. Since the changes in the granulocytic counts are so definitely related to those of the reticulocytes, and since the return of the granulocytes to the circulation is associated with development of an eosinophilia, it seems that the granulopenia must be a phenomenon in the genesis of blood cells in the bone marrow.

**Summary and Conclusions.** Data related to hematopoietic regeneration are correlated from total and differential counts of the

erythrocytes, reticulocytes, and white cells, which were made throughout the course of treatment with quinine of 4 sisters with estivo-autumnal malaria.

A definite sequence is found in the regeneration of the elements formed in the bone marrow, *viz.*: reticulocytes, erythrocytes, neutrophils, eosinophils. The lymphocytes, basophils and large mononuclear cells were unaffected.

A reticulocytosis followed defervescence and the disappearance of asexual forms of parasites, and it was synchronous with the appearance of gametes. The number of reticulocytes was increased by the eighth day of treatment, reached a peak by the eleventh day, remained at a plateau until the nineteenth day, and then began to fall.

The number of erythrocytes had begun to fall by the eighth day of treatment, that is, when the reticulocytes were definitely rising. They continued to decrease to low levels until the nineteenth day of treatment, that is, until the time that the reticulocytes began to fall.

The number of leukocytes remained stationary at normal levels until the twelfth day of treatment, that is, until the reticulocytes reached a peak. They then began to progressively decrease until the nineteenth day of treatment, that is, until the reticulocytes began to decrease. At that time they began to return to normal, accompanied by an eosinophilia. The changes in the leukocyte counts were due to changes in the neutrophils.

The temporary granulopenia is considered probably a genetic phenomenon because of its relationship to the changes in the reticulocytes and to the total red cells, and because of the development of an eosinophilia at its cessation.

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## MAINTENANCE OF THE SEDIMENTATION RATE OF ERYTHROCYTES IN VITRO IN CASES OF MALIGNANT TUMORS AND HODGKIN'S DISEASE.

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It has been shown by numerous investigators that the sedimentation rate of erythrocytes in blood that is left standing at room temperature begins to decline after the first few hours and reaches extremely low, at times hardly readable, values at the end of 24 hours.<sup>2b</sup>

No exceptions to this were noted until recently, when Koster<sup>3a</sup> reported that in certain specimens of blood the sedimentation rate remains the same throughout the 24 hours and that in others it may even become accelerated significantly within the first 6 hours, or progressively throughout the 24-hour period. Such exceptional changes in the sedimentation rates of erythrocytes he found only in the bloods of patients who have malignant tumors or Hodgkin's disease, or who have been given certain drugs, such as potassium iodide, bismuth, salvarsan, aminopyrine, lipiodol, perabrodil, oral tetragnost, and, as we have since found, also sulphanilamide and sulphapyridine.

When Koster applied the results of this observation to the study of serial sedimentation rates of erythrocytes in the diagnosis of malignant tumors, he found the results to be 95% positive (*i. e.*, rate maintained) in 112 cases of malignant tumors, and 100% in 14 cases of Hodgkin's disease. In 100 normal persons and in 460 pathologic but non-malignant conditions, the sedimentation rate declined essentially in accordance with previous observations.

Since any aid in diagnosis of malignant tumors is to be welcomed, especially if that aid is a simple procedure which can be carried out by any medical practitioner, it was deemed worth while to repeat Koster's work.

**Method.** The technique employed was as follows: 8 cc. of venous blood were mixed with 2 cc. of freshly prepared 3.8% sodium citrate in a graduated test tube. This constituted the store of blood from which Wintrobe sedimentation tubes were filled directly after the blood was drawn, then after 1, 2, 3, 4, 5, 6 hours, and finally after 24 hours. The blood was thoroughly mixed each time before removing specimens for sedimentation tests, since the red cells settle out between tests. The temperature of the room where the blood was kept and the tests carried out was fairly constant. All the readings were made exactly 1 hour from the time of filling the sedimentation tube. The sedimentation tubes were carefully cleaned and dried before use. Many tests were set up in duplicate and triplicate, especially in those bloods which had a slow sedimentation rate. The greatest variation in readings seldom exceeded 2 mm. This is in agreement with the results of Ham and Curtis<sup>2a</sup> on duplicate determinations.

It should be noted that our technique is essentially that of Koster, except for the difference in the mixing of the blood, and in the use of the Wintrobe instead of the Westergren tube. These changes in no way affected the results. Sample data obtained with this method are given in Table 1.

TABLE 1.—SERIAL SEDIMENTATION RATES IN STORED CITRATED BLOOD.

Diagnosis.	Directly after blood is drawn.	After 1 hour.	After 2 hours.	After 3 hours.	After 4 hours.	After 5 hours.	After 6 hours.	After 24 hours.
Normal individual . . . . .	8	8	7	7	6	3	2	1
Diabetes mellitus . . . . .	25	25	24	24	20	16	12	3
Carcinoma of stomach . . . . .	11	11	10	11	11	12	12	13
Carcinoma of lung . . . . .	65	64	64	65	64	64	65	63
Carcinoma of esophagus . . . . .	38	39	44	43	35	35	26	18
Hodgkin's disease . . . . .	60	61	60	64	62	62	61	59

**Materials.** Patients in the medical and surgical wards of this hospital constituted the majority of cases which furnished the blood for the sedimentation tests. A few cases from the out-patient department, as well as several from private sources, are included in this series. Only a few with obvious malignant disease were selected for testing. The rest, for the most part, were routine admissions, some of which presented problems in differential diagnosis where either a malignant tumor or Hodgkin's disease was also considered. Particular care was taken to exclude any case from the records in which the administration of drugs might have influenced the result of the tests.

Whenever a *positive* sedimentation curve was obtained in a patient, *i. e.*, one which could be interpreted as denoting a malignant tumor or Hodgkin's disease, the diagnosis was confirmed either by surgery, biopsy or autopsy. Only a few cases with negative sedimentation curves could be followed up in such a manner because the majority of them improved clinically.

In this manner serial sedimentation tests were done for a period of  $2\frac{1}{2}$  years.

**Results.** Data on 176 cases are presented. The important facts are arranged in Table 2.

TABLE 2.—DIAGNOSTIC ACCURACY OF SERIAL SEDIMENTATION CURVES.

	Number.	With positive sedim. curve.	With negative sedim. curve.	Percentage accuracy.
Proven malignant cases . . . . .	118	113	5	95.7
Proven cases of Hodgkin's disease . . . . .	3	3	0	100.0
Non-malignant cases . . . . .	55	3	52	94.6
Total . . . . .	176			

Of the 5 cases of malignancy with the negative sedimentation curves or false negatives, 1 was a carcinoma of the lung, 3 were carcinomas of the stomach and 1 was a carcinoma of the transverse colon. In 2 of these cases the sedimentation studies were done twice and both times yielded essentially the same results.

Concerning the 3 non-malignant cases with positive curves, or false positives, where drug effects could be more or less definitely eliminated, one was an elderly woman with hypertrophic arthritis and moderately severe anemia. The second was also an elderly woman with pernicious anemia, who came to the hospital in a very debilitated state, but responded subsequently to liver therapy with much improvement. The third was a luetic woman with a clinical picture of carcinoma of the stomach, which, however, was not confirmed by operation and autopsy.

The further courses of the first 2 cases are being followed with much interest.

From the numerous cases in which the serial sedimentation test coincided with the pathologic diagnosis, but was at variance with the clinical diagnosis, a few records are given:

CASE 1.—C. F., aged 73 years, male, admitted on August 2, 1938, complaining of increasing jaundice and pruritus, chilly sensations, epigastric pain and anorexia for the past 8 days; and clay-colored stools and vomiting for the preceding 6 days. The jaundice and pruritus had increased markedly 24 hours before admission.

Past history was negative except for an attack of weakness and palpitation about 8 years ago. The family history revealed the interesting fact that in 1935 a son of this patient had died of a cancer of the pancreas after an operation.

Physical examination on admission: temperature 100.2°, pulse 70, respirations 24 per minute, blood pressure 150/74 mm. of mercury. The sclerae and skin were deeply jaundiced. Excoriations were visible all over the body but were especially numerous over the anal cleft. The thorax was emphysematous and the lungs hyperresonant. A faint systolic blow was heard near the apex of the heart. There was slight muscle spasm in the right upper abdominal quadrant with tenderness maximal in the mid-clavicular line 3 finger-breadths below the costal margin. The edge was irregular and felt firm but slightly tender. A globular, fairly firm, but fluctuant mass the size of an egg was felt 3 finger-breadths below the costal margin just beyond the midclavicular line. This mass seemed somewhat distinct from the liver, was tender and moved with respiration. Both legs showed varicose veins. The peripheral arteries were sclerotic. The prostate gland was moderately enlarged, soft, and slightly irregular.

*Laboratory Data.* Bile was found in the urine, but not in the stool; icterus index rose in 2 days from 71 to 189 units; total cholesterol, 133 mg. per 100 cc. blood; cholesterol esters, 51%; phosphatase, 16.5 units; non-protein nitrogen, 44 mg. per 100 cc. blood; total proteins, 6.66 gm. per 100 cc. blood, with an A/G ratio of 0.90.

*Course.* Direct Roentgen ray study of the gall bladder revealed no evidence of calculi. After the oral administration of iodeikon, the gall bladder failed to visualize. The finding was indicative of a hepatic or biliary lesion. The clinical impression of the case was that of a carcinoma of the head of the pancreas. On August 8, 1938, a serial erythrocyte sedimentation curve was interpreted to mean that there was no malignancy present. Jaundice was increasing steadily. An exploratory operation followed by a cholecystostomy was done on August 13. The gall bladder was found to be distended to the size of a lemon, tense, but free of calculi. The common duct was distended, and again no stone was felt. No masses were palpated in the pancreas. The gall bladder was drained and a probe passed from

the cystic duct into a distended common bile duct, which could not get through into the duodenum.

Although the immediate postoperative condition of the patient was good, on the night of August 15 his pulse became irregular, coarse râles appeared at the base of the right lung. His condition became poor, the fibrillation persisted, and he expired on the morning of August 17. The postmortem diagnosis was: chronic interstitial pancreatitis with fibrosis; stenosis of common bile duct; arteriosclerotic heart disease.

**Comment.** In this case the clinical impression of a malignant growth had much in its favor; but the serial sedimentation curve pointed in the direction of the correct diagnosis.

**CASE 2.**—L. W., aged 40 years, female, colored, first came to the O.P.D. of this hospital in 1937, complaining of polyuria and loss of weight. On investigation, she was found to have diabetes mellitus and also a positive Wassermann reaction. Her diabetes had been treated with diet and insulin. She received several courses of antiluetic therapy. In May, 1937, a spinal fluid Wassermann was negative.

She was admitted to another hospital in April, 1938, complaining of a cough that had lasted 3 weeks. The blood pressure at that time was 190/120. The diagnosis was left pleural effusion, etiology unknown. Investigation for tuberculosis, including guinea pig inoculation, was negative. A diagnosis of diabetes mellitus and fibromyomata uteri was also made. She was discharged from the hospital after 1 month.

In June, 1938, she was admitted to a second hospital for similar complaints. The diagnosis was left hydropneumothorax, diabetes mellitus and fibromyomata uteri. Investigation for tuberculosis was negative.

In August, 1938, she was admitted to this hospital with the complaint of dyspnea on effort and cough. She was found to have a left pleural effusion. This was tapped several times. Repeated investigation and guinea pig inoculations were all negative for tuberculosis.

On August 24, the serial erythrocyte sedimentation test (Koster) was positive for malignancy. On September 9, a thoracoscopy was done. This revealed an area of granulation tissue on the posterior parietal wall surrounded by some small hemorrhagic cyst-like areas. No diagnosis was warranted from this evidence. The opinion that the pleural effusion and the fibromyomata might be linked together as in Meigs' syndrome was strongly entertained and a hysterectomy was performed. After all these procedures, the patient was discharged markedly improved in her general condition.

For 7 months thereafter she got along quite well. On May 20, 1939, she was readmitted to this hospital with complaints of dyspnea, pains in various joints of the body and pain in the chest. There was no cough or bloody sputum.

*Physical Examination.* Temperature 101, pulse 92, and respirations 22 per minute, blood pressure 140/90 mm. of mercury. She was slightly dyspneic. The fundi showed fairly advanced sclerosis of vessels. Several patches of exudate and a few recent hemorrhages were seen in both fundi. The disks were normal. The throat was moderately congested. The tonsils showed evidence of chronic inflammation. There was poor oral hygiene. The tongue was coated and teeth carious. The thorax revealed a diminution in mobility of the left side. There were râles at the right base. In the left chest there was absent tactile fremitus anteriorly and posteriorly almost up to the apex, dullness to flatness to percussion, and absent breath sounds. The left border of the heart could not be made out due to flatness of the left chest. The right border was about 6 cm. to the right of the sternum. The heart rate was rapid, with a gallop rhythm. A to-and-fro



friction rub was heard best at the base of the sternum. No murmurs could be made out. The abdomen was soft. The liver was moderately enlarged. There was a 2+ sacral edema. In the pelvis a small nodule was palpated in the left fornix, possibly the left ovary. Rectal examination was negative. A *hard lymph node* was felt in the left axilla.

Examination of the blood revealed a hypochromic anemia with a moderate leukocytosis; the urine showed a 2+ albuminuria and 0.2% sugar. The blood Wassermann reaction was negative.

The axillary lymph node was excised. On section it showed metastatic carcinoma. A bronchoscopy performed on June 8, 1939, revealed the presence of a granuloma in the left bronchus. The right bronchus was normal.

**Comment.** In this case the main diagnosis rested between a polyserositis and a malignancy of the pleura. The serial sedimentation of erythrocytes test pointed in the direction of the correct diagnosis 10 months before the biopsy definitely confirmed it.

**Discussion.** The application of the sedimentation rate of erythrocytes test to the diagnosis of malignancy is not new.<sup>1</sup> Heretofore the rapidity of the sedimentation rate was regarded as the diagnostic factor in the use of the test. However, as it can be shown readily that many cases of undoubted cancer are accompanied by slow sedimentation rates, the usefulness of the test as a diagnostic procedure becomes limited.

The method described here does not depend on the rapidity of the sedimentation rate, but on the maintenance of a certain sedimentation rate level throughout a period of 24 hours.

What is the basis of this test? It has been suggested<sup>3b</sup> that the exceptional behavior of the sedimentation rate of blood depends on changes in the red blood cells in patients suffering from malignant tumors, whereby its property of retaining potassium ions for a long period when stored with its plasma is altered; whereas the cell from the non-cancerous patients does not possess this property. But the experimental evidence brought forth to demonstrate the above-mentioned assumption is insufficient. A small number of our own experiments also failed to corroborate it. Thus the basis for this test remains unexplained, and therefore the mechanism, whatever it is, remains to be determined.

Regarding the practical value of this test, however, we feel that the data of Koster, corroborated in this work, justify the hope that it may become a real aid in the diagnosis of malignant disease.

Many questions are yet to be answered before the usefulness of this test can be fully appraised. The most important question is that dealing with the effect of drugs on the character of the sedimentation curve. In the course of our study we noticed that sulph-anilamide and sulphapyridine influence the sedimentation curve in a manner similar to the drugs enumerated by Koster. Another question is how soon after a malignant growth has started in the body does the sedimentation curve become affected and how soon after the removal of that growth does the curve change its character.

Many more questions suggest themselves, but answers must be deferred to future studies.

Our purpose has been to investigate the data of Koster in order to find out whether the serial sedimentation rate by his method may be of value in the diagnosis of malignant tumors. We believe that the data presented warrant an affirmative answer.

**Summary.** A study was made of 176 cases, of which 118 were proven malignancies and 55 were pathologic conditions other than malignancies. The percentage of positive results (maintenance of the sedimentation rate) in the malignant cases was 95.7% and of negative results was 94.6% in the cases of non-malignant disease. Data are presented to show that the maintenance of the sedimentation rate of erythrocytes in drawn blood over many hours (Koster method) may be of much practical value to the clinician as an aid in diagnosis of malignant tumors and Hodgkin's disease. The reason for this exceptional behavior has not been explained.

#### REFERENCES.

- (1.) Behan, R. J.: Cancer, St. Louis, The C. V. Mosby Company, p. 308, 1938.
- (2.) Ham, T. H., and Curtis, F. C.: (a) *Medicine*, 17, 457, 1938; (b) *Ibid.*, p. 462.
- (3.) Koster, L.: (a) *Acta med. Scand.*, 93, 420, 1937; (b) *Ibid.*, p. 427.

## BOOK REVIEWS AND NOTICES

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**CLINICAL PARASITOLOGY.** By CHARLES FRANKLIN CRAIG, M.D., M.A. (HON.), F.A.C.S., F.A.C.P., Colonel United States Army (Retired), D.S.M., Emeritus Professor of Tropical Medicine in the Tulane University of Louisiana, New Orleans, and ERNEST CARROLL FAUST, M.A., PH.D., Professor of Parasitology in the Department of Tropical Medicine, Tulane University of Louisiana, New Orleans. Pp. 772; 244 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, \$8.50.

THE second edition of this book within three years after its first appearance indicates very well the place that it fills in the literature of parasitology. This edition has been increased by some 40 pages, part of which is occupied by a new chapter on the leeches (Hirudinea). The character of other changes do not warrant detailed consideration. It is enough to say the book certainly is the equal of any available today. H. R.

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**THE SOLDIER'S HEART AND THE EFFORT SYNDROME.** By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Physician, University College Hospital; Honorary Consulting Physician to Ministry of Pensions, etc. Pp. 103. Second edition. London: Shaw & Sons, Ltd., 1940. Price, 8s, 6d.

THIS concise practical manual on heart disease in soldiers covers the subject from the examination of recruits to making medical reports at the time of their discharge. Five of the eight chapters deal with the effort syndrome. They contain a description of the condition; a discussion of methods by which it can be diagnosed, and its severity determined; also valuable hints concerning the recognition of malingery. The chapter on prognosis and treatment is based upon follow-up studies of individuals who had the effort syndrome during the first World War. The follow-up period covers only the first five years after discharge, so there are no figures concerning the liability of these individuals to degenerative cardiovascular disease.

There is no better book on the subject. It should be especially useful to officers in the Army Medical Corps who are called upon to make decisions in the field of heart disease. F. W.

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**MANAGEMENT OF THE CARDIAC PATIENT.** By WILLIAM G. LEAMAN, JR., M.D., F.A.C.P., Assistant Professor of Medicine in Charge of the Department of Cardiology, Woman's Medical College of Pennsylvania, Philadelphia; Cardiologist, Women's College, Memorial, Northeastern Hospitals, and Philadelphia Hospital for Contagious Diseases, etc. Pp. 705; 255 illustrations. Philadelphia: J. B. Lippincott Company, 1940. Price, \$6.50.

MANY books are recommended as being particularly useful to the general practitioner. Few can be said to fulfil their promise; this one does.

It is an inclusive treatise on heart disease, giving details of management, and presenting many illustrative case reports. Certain sections have been written for the author by recognized authorities in their especial fields. Clarity and sound judgment characterize the book. By way of minor

criticism, it is regretted that sulfapyridine was not given sufficient credit for the part it played in the recovery of a patient having pneumococcic empyema and pericarditis, and known to the Reviewer (p. 175). Orthostatic hypotension is not included among the rarer causes of syncope, nor is the disorder always characterized by "no compensatory increase in the pulse rate" (p. 434).

W. J.

**THE VIRUS. Life's Enemy.** By KENNETH M. SMITH, F.R.S. Pp. 176; 1 illustration. New York: The Macmillan Company, 1940. Price, \$2.00.

THE importance of viruses as disease-producing agents is becoming ever more widely recognized. But it is only during the past twenty years that decisive progress has been made in our knowledge concerning these pathogens. Indeed it is probable that many physicians, who graduated as recently as 10 years ago, heard no lectures on viruses during their medical school days. In any case it is quite certain that the medical profession in general is inadequately informed, and for this reason it is desirable to have available a brief but accurate text which may serve as an introduction to the relatively new science of viruses.

The author is a well-known investigator at one of the virus research centers in Great Britain. He has been able to bring together a readable, instructive and thoroughly modern account of the viruses, their nature and their action. His book may highly be recommended to physicians and biologists in general as a good first guide to a fascinating and important group of things.

B. L.

**A MANUAL OF THE COMMON CONTAGIOUS DISEASES.** By PHILIP MOEN STIMSON, A.B., M.D., Assistant Professor of Clinical Pediatrics, Cornell University Medical College; Visiting Physician, Willard Parker Hospital, etc. Pp. 463; 54 illustrations and 6 plates (4 in color). Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, \$4.00.

AN excellent, practical and convenient little volume that is highly recommended both to practitioners and students. A third edition testifies to its popularity.

R. K.

**PHYSICAL DIAGNOSIS.** By WILLIAM NANCE ANDERSON, B.Sc., M.D., Associate Clinical Professor of Medicine at the University of Southern California School of Medicine, Los Angeles. Pp. 424; 92 illustrations. Philadelphia: Lea & Febiger, 1940. Price, \$4.75.

FOLLOWING a chapter of historical background, Part I, *Fundamental Principles of Physical Diagnosis*, opens with a discussion of the clinical history and its interpretation. The next 64 pages are devoted to the four common methods of examination—inspection, palpation, percussion, and auscultation—under both normal and abnormal conditions. The physical principles which underlie the production and alteration of sound in the normal and in the diseased lung are not stressed, although the author does include several quotations from Skoda's works.

Part II, on the *Physical Examination*, begins with an excellent section on general impressions, the head, the neck, and the extremities—those parts so often slighted by students, whose chief interest centers in examination of the thorax. The chapters devoted to the heart and the lungs amplify points already covered in Part I. A section on *Special Examinations* describes briefly such assorted procedures as genito-urinary and rectal examinations, gastric analysis, the rudiments of neurologic examination, ophthalmoscopic and laryngoscopic examinations, roentgenologic study of the thorax and abdomen, and electrocardiography.

Part III, comprising more than a third of the book, is devoted to Physical Diagnosis in Disease. Here the author attempts to describe the important clinical features and physical findings present in over 200 diseases and pathologic conditions; the individual sections vary in length from several pages to a few lines.

S. L.

**A TEXTBOOK OF LABORATORY DIAGNOSIS.** With Clinical Applications for Practitioners and Students. By EDWIN E. OSGOOD, M.A., M.D., Associate Professor of Medicine and Head of the Division of Experimental Medicine, University of Oregon Medical School, and Member of the Staff of Multnomah County Hospital, etc. Pp. 676; 27 text illustrations and 9 colored plates. Third Edition. Philadelphia: The Blakiston Company, 1940. Price, \$6.00.

As in previous editions, the subject matter of this book has been divided into two parts. In Part One the disorders of the different systems are considered with a brief discussion of the essential points in the anatomy, physiology, biochemistry and pathology at the beginning of the respective chapters. Part Two deals with laboratory methods and includes an Index by Diseases, which is a valuable aid in the rapid planning of a laboratory study, and an Author Index in addition to the Subject Index. The chapters on hematology have been revised into three parts with additions made to each division. The author has attempted to clarify the confused nomenclature of the erythropoietic system and with good reasoning has chosen new names for cells of different series. Fortunately, the more commonly used term is given in parentheses after the newer terminology so that the reader can familiarize himself with the latter without frequent reference to an explanatory table at the beginning of the chapter.

In the discussion of the examination of the bone marrow, the technique and interpretation of sternal aspiration is given with no mention of the method of removing a button of sternal marrow for histologic sectioning and differential staining. In inexperienced hands the interpretation of material obtained by aspiration from the marrow, spleen or lymph nodes may meet with considerable difficulty and surely the removal of a lymph node for histologic section would be preferable, under most circumstances, to a needle puncture of the node.

These minor criticisms are more than compensated by the clear presentation of a great deal of material in a relatively brief manner. Where more information might be desired on a given subject, frequent references to recent literature are placed at the bottom of the page and an additional bibliography is included at the end of each chapter. The 9 colored plates are excellent. The book is highly recommended as a guide in laboratory diagnosis and procedure.

H. D.

**TEXTBOOK OF BIOCHEMISTRY.** By BENJAMIN HARROW, PH.D., Professor of Chemistry, City College, College of the City of New York. Pp. 439; 88 illustrations. Second Edition, revised. Philadelphia: W. B. Saunders Company, 1940. Price, \$3.75.

THIS second edition is enlarged to include more complete discussion of some subjects (enzymes, foods, hormones, sterol chemistry, protein structure, etc.) and to incorporate new material such as our new knowledge of the chemical constitution of the virus of tobacco mosaic, and of bacteriophage, progress in the chemistry of the vitamins, the use of isotopes in metabolism studies, and so on.

Students of the medical sciences will find the book most useful. It is simply and clearly written, and the references at the end of each chapter to the current literature encourage the reading of reviews and original papers.

E. W.

THE VARIETIES OF HUMAN PHYSIQUE. An Introduction to Constitutional Psychology. By W. H. SHELDON, PH.D., M.D., Harvard University. With the collaboration of S. S. STEVENS, PH.D., Harvard University, and W. B. TUCKER, M.D., University of Chicago. Pp. 347; 104 illustrations. New York: Harper & Bros., Publishers, 1940. Price, \$4.50.

OBSERVATION of variations in human build, and interest in the relation of such variations to temperament and to disease susceptibility, are as old as science. Sheldon and his associates start with the old divisions into phthisic and apoplectic, asthenic and pyknic, and develop the concept of three principal morphologic components of physical build combined in varying degree to produce a large number of recognizable physical types. Their first component, endomorphy, "means relative predominance of soft roundness"; the second component, mesomorphy, "means relative predominance of muscle, bone, and connective tissue"; and third, ectomorphy, "means relative predominance of linearity and fragility." They then assign arbitrary grades to the proportion of each component in the physical makeup of an individual, rating the grades by numbers from one to seven. Thereby, they arrive at a large number of "somatotypes," each identified by a number expressing the relative proportion of each component (*e. g.*, 711, 325, and so on). Some of these somatotypes are of only theoretical occurrence; they describe the actual observation of 76. In addition, they consider variables such as gynandromorphy, or the bisexuality of a physique, and texture, or degree of fineness or coarseness of structure. The authors have developed their own anthropometric method which depends on the measurement of photographs taken under standard conditions. Heretofore, techniques in physical anthropometry have been based upon the methods of Rudolf Martin, which use bony points as landmarks for measurement. Sheldon's technique is thus a radical departure, as it depends upon the measurements of soft part outlines in the photograph more than osseous landmarks. In their technique of anthroposcopy it is necessary to grade the degree of various components by inspection of the photograph as well as by consideration of derived indices. The possibility of lack of objectivity is obvious, but the authors go to great length to explain the precautions they have developed against this disadvantage. Their subjects consisted largely of college students, presumably healthy males in the late 'teens and early twenties; they made only occasional excursions into studies of later years, pathologic states, and the opposite sex. After an extensive description of their somatotypes, the authors set themselves to highly interesting speculations upon such aspects as the problem of norms; the influence of heredity; the influence of endocrine function; the relation of the constitution to temperament, to mental disorder, to susceptibility to physical disease, and to many other variables in the human organism. For instance, the authors suggest that proper diet for one somatotype may be another somatotype's poison; that constitution as well as temperament influence choice in clothing and taste in architecture. They see possibilities for avoidance not only of crime but of domestic discord, if one can predict from an individual's somatotype, and hence his temperament, what worldly pitfalls he should avoid or what type of young woman he should seek out as a mate.

The authors do not pretend to have reached any conclusions. To be complete such study must proceed over a period of years and encompass many, many thousands of observed subjects—possibly it must span generations. Nevertheless a question which has attracted scientific and philosophic attention for so long a time as has this question of the relation of physical build to temperament and disease, deserves unlimited work and perseverance, if only these are feasible.

This is a fascinating book; a bit heavy it may be, but not dry. After

reading a few chapters the Reviewer found himself trying to guess at the somatotypes of patients, of colleagues, and of casual strangers on the street. The style is, in view of the long detailed descriptions of types, remarkably clear, concise, and at times even sparkling. The many photographs of somatotypes supplement the descriptions well, but some of these photographs seem to have lost detail in the process of reproduction. The paper and type are satisfactory for easy reading. J. C.

HEIL HUNGER! HEALTH UNDER HITLER. By DR. MARTIN GUMPERT. Translated from the German by MAURICE SAMUEL. Pp. 128. New York: Alliance Book Corporation, 1940. Price, \$1.75.

ACCORDING to the claim made on the wrapper, this volume "studies the effect of the Nazi régime on the health of the German people. Setting aside discussion of political, racial, or religious controversies, it shows clearly the degeneracy and illness that have resulted from the present situation in Germany. For six years Germany has lived under what amounts to war-time conditions and is today found in such a weakened physical state that it is doubtful if her people can from a physical standpoint endure much more privation" . . . . It is stated furthermore that the "book is based exclusively on . . . . medical statistics in technical German magazines and the like. Neither propaganda material nor mere suspicion colors his findings."

Even if these claims were thoroughly substantiated in the text, it is difficult to understand how and why such a volume could be interesting to intelligent persons living in a neutral nation. Maybe the implication is that the horrible example here set up should warn all other people against the system which has produced the results culled out of "medical statistics in technical German magazines . . . ." Sometimes, however, our reactions are conditioned on reflexes which cannot be foretold. The bare facts (if statements found in this volume ever were factual) without the added ingredient, against which the author protests, might arouse emotions not at all intended—they might have excited profound pity in us. We might even have gone to the extent of raising funds to buy arch supports for the greatly increased numbers of people who are now found to have flat feet. As a matter of fact the "added ingredient" is not omitted. It is obviously expected of the reader that he shall go through these pages with mounting disgust.

Whether or not readers are likely to have been found, who were so uncritical as to react at all, in either direction, is to this Reviewer the only serious question there is about the book—and this is one not serious. Statistical studies and reports are, we like to believe, based upon canons which are inviolable. This volume violates nearly all of them.

A. H.

THE HYPOTHALAMUS and Central Levels of Autonomic Function. Proceedings of the Association December 20 and 21, 1939, New York. Vol. XX of Research Publications Association for Research in Nervous and Mental Disease. Editorial Board: JOHN F. FULTON, M.D., Chairman, S. WALTER RANSON, M.D., ANGUS M. FRANTZ, M.D. Pp. 980; 319 illustrations and 35 tables. Baltimore: The Williams & Wilkins Company, 1940. Price, \$10.00.

THE reader is impressed by the amount of work that has been accomplished in just one narrow field of medicine in the 30 years that have passed since the first investigations into the significance and physiology of the hypothalamus commenced. The present volume lists more than 1300 references, an average of one paper on the hypothalamus a week during the

last 30 years. The book unites 35 contributions to anatomy and physiology of the hypothalamus and its clinical syndromes, read before the last meeting of the Association for Research in Nervous and Mental Diseases. In the first part phylogenetic and embryologic development of the hypothalamic region are discussed, the arrangement of its nuclei and their connections with other parts of the nervous system and the pituitary gland. In addition, 20 photomicrographs of various planes of the hypothalamus show the exact location of its nuclei in several animals and man. A commission has organized for the first time the confused nomenclature of the structures of this area. The second part of the volume deals with the rôle of the hypothalamus in regulating temperature, water, fat and carbohydrate metabolism, cardiovascular and gonadotropic function, and also with the hypothalamic control of pituitary function. The third part of the symposium is concerned with pathologic changes observed in the hypothalamus in organic diseases and major psychoses, and conversely with clinical syndromes occurring in hypothalamic diseases and tumors. More than 300 photomicrographs, drawings and diagrams illustrate the articles. This is a book for specialists, such as neuroanatomists, neurophysiologists and clinical neurologists; it will be indispensable to them as an invaluable source of information and as a starting point for further research.

F. L.

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INJURIES OF THE SKULL, BRAIN AND SPINAL CORD. Neuropsychiatric, Surgical, and Medico-Legal Aspects. Edited by SAMUEL BROCK, New York University. Contributors: BERNARD J. ALPERS, ABRAHAM BLAU, KARL M. BOWMAN, SAMUEL BROCK, JEFFERSON BROWDER, BRONSON CROTHERS, LEO M. DAVIDOFF, THOMAS K. DAVIS, CHARLES DAVISON, CORNELIUS G. DYKE, CHARLES A. ELSBERG, A. R. ELVIDGE, E. D. FRIEDMAN, FRANCIS C. GRANT, CLARENCE C. HARE, GEORGE B. HASSIN, MOSES KESCHNER, MAX M. PEET, W. RITCHIE RUSSELL, PAUL SCHILDER, C. P. SYMONDS. Pp. 632; 63 illustrations. Baltimore: The Williams & Wilkins Company, 1940. Price, \$7.00.

This book is a pertinent contribution to one of the increasingly urgent problems of the day—head injuries. Traffic accidents, industrial traumata, war injuries and their economic and forensic implications concur in stressing the need for an authoritative guide through the intricate system of their diagnosis, their immediate and later surgical, medical and psychiatric treatment and through the aftermath of justified and unjustifiable compensation and indemnity claims. Twenty-two specialists have contributed their experience in the various phases of the problem. Alpers discusses birth injuries to the brain, Bronson Crothers to the spinal cord, both pointing to the not sufficiently accepted responsibility of the obstetrician and the inherent risk of spontaneous and instrumental trauma to skull and vertebrae during birth; on the other hand, they reduce to correct proportion the over-emphasized rôle of asphyxia as an etiologic factor of retarded development imbecility. The greater space is naturally dedicated to brain injuries proper and their sequelæ. Samuel Brock gives a survey of the whole problem. He discusses the divergent nomenclature, the specific requirements of the history, of the methods of examination and treatment and coördinates the different chapters. G. B. Hassin describes and illustrates the histopathologic changes underlying concussion, contusion and vascular lesions. Jefferson Browder outlines the topic of fractures of the skull, the complicating osteomyelitic infections and epidural abscess; and C. G. Dyke the roentgenologic aspects of skull fractures, aided by 26 instructive Roentgen ray pictures. A detailed chapter by C. P. Symond deals with concussion, contusion of the brain in terms of neurophysiology and pathology, with the specific means of obtaining a correct diagnosis, and with the



treatment of the basic condition as well as of accompanying symptoms and signs. W. R. Russell treats of the injuries of the cranial nerves; E. D. Friedman of traumatic intracerebral hemorrhages. M. M. Peet debates the important question of extradural and subdural hematomata and their treatment; F. C. Grant, post-traumatic brain abscess and meningitis; L. M. Davidoff, the handling of gunshot wounds and of foreign bodies in the brain, supplementing the experiences of the last war by peace time observations. Post-traumatic epilepsy, neuroses and psychoses are extensively dealt with by A. R. Elvidge, P. Schilder, K. M. Bouman and Abram Blau respectively. The excellent paper of C. A. Elsberg on injuries of the spinal cord and its nerve roots reflects the author's great personal experience. Chapters on the relationship of brain injuries to other organic brain diseases by I. S. Wechsler; of spinal cord injuries to other diseases of the cord by T. K. Davis; of the pathology of spinal cord injuries by Charles Davison; on the effect of electric shock, of fat and air embolism upon the nervous system, and on caisson disease by C. C. Hare round out the subject. The two chapters by Moses Keschner on malingering in connection with and the medico-legal aspects of injuries of skull, brain and spinal cord deserve special recommendation. These complex topics are described so intelligibly and comprehensively in all their medical and juridical ramifications as it can be expected only by someone who is an experienced M.D. and an L.B. at the same time. Useful bibliographies are added to most of the chapters. Whoever in the medical profession is concerned with injuries of the central nervous system and their consequences, including the general practitioner, the internist, neurologist, psychiatrist and surgeon, the obstetrician and pediatrician as well as the pathologist and roentgenologist, the industrial and the insurance physician, will welcome this up-to-date handbook.

F. L.

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### NEW BOOKS.

*Methods for Diagnostic Bacteriology.* A Complete Guide for the Isolation and Identification of Pathogenic Bacteria for Medical Bacteriology Laboratories. By ISABELLE G. SCHAUB, A.B., Assistant in Bacteriology, Department of Pathology and Bacteriology, The Johns Hopkins University School of Medicine, and M. KATHLEEN FOLEY, A.B., Bacteriologist in Charge of the Diagnostic Bacteriological Laboratories of the Medical Clinic, The Johns Hopkins Hospital, Baltimore. Pp. 313. St. Louis: The C. V. Mosby Company, 1940. Price, \$3.00.

*The Histamine and Insulin Treatment of Schizophrenia and Other Mental Diseases.* By HORACE HILL, M.R.C.P., Medical Superintendent, Laverstock House Mental Home, Salisbury. Pp. 133. Baltimore: The Williams & Wilkins Company, 1940. Price, \$1.75.

*Surgery of the Hand.* By R. M. HANDFIELD-JONES, M.C., M.S., F.R.C.S., Surgeon to Outpatients, St. Mary's Hospital; Senior Surgeon, Florence Nightingale Hospital, etc. Pp. 140; 95 illustrations (several in color). Baltimore: The Williams & Wilkins Company, 1940. Price, \$4.50.

*Congenital Syphilis.* By CHARLES C. DENNIE, B.S., M.D., Professor of Dermatology, University of Kansas Medical School, Kansas City, Kan.; Chief of the Department of Dermatology and Syphilology of Bell Memorial Hospital, Kansas City, Kan., etc., and SIDNEY F. PAKULA, B.S., M.D., Visiting Pediatrician to Children's Mercy Hospital, Kansas City General Hospital, Alfred Benjamin Clinic, and Menorah Hospital, Kansas City, Mo. Pp. 596; 133 illustrations. Philadelphia: Lea & Febiger, 1940. Price, \$8.00.

*Multiple Human Births.* Twins, Triplets, Quadruplets and Quintuplets. By HORATIO HACKETT NEWMAN, PH.D., Sc.D., Professor of Zoology, University of Chicago. Pp. 214; illustrated. New York: Doubleday, Doran & Co., Inc., 1940. Price, \$2.50.

*The Neuroses in War.* By Several Authors under the Editorship of EMANUEL MILLER, M.A. (CANTAB.), M.R.C.P., D.P.M. (CAMBS.), with a concluding chapter by H. CRICHTON-MILLER, M.D., F.R.C.P. Pp. 250. New York: The Macmillan Company, 1940. Price, \$2.50.

*Synopsis of Materia Medica, Toxicology, and Pharmacology.* For Students and Practitioners of Medicine. By FORREST RAMON DAVISON, B.A., M.Sc., PH.D., M.B., Assistant Professor of Pharmacology in the School of Medicine, University of Arkansas, Little Rock. Pp. 633; 45 illustrations (4 in color). St. Louis: The C. V. Mosby Company, 1940.

*The Theory and Practice of Anæsthesia.* By M. D. NOSWORTHY, M.A., M.D., B.CH. (CANTAB.), Anæsthetist to Westminster Hospital; Anæsthetist to Grosvenor Hospital for Women; late Senior Resident Anæsthetist, St. Thomas's Hospital, with a Foreword by I. W. MAGILL, M.B., B.CH. (BELFAST), Senior Anæsthetist to Westminster Hospital; Anæsthetist to Brompton Hospital for Consumption and Diseases of the Chest. Pp. 223; 35 illustrations. New York: Chemical Publishing Company, 1940. Price, \$4.25.

*A Treatise on Medicolegal Ophthalmology.* By ALBERT C. SNELL, M.D., Lecturer in Ophthalmology, School of Medicine and Dentistry, University of Rochester; Consultant in Ophthalmology, Strong Memorial and Rochester General Hospitals, etc. Pp. 312; illustrated. St. Louis: The C. V. Mosby Company, 1940.

*A Surgeon's Life.* The Autobiography of J. M. T. FINNEY. Pp. 396; 1 illustration. New York: G. P. Putnam's Sons, 1940. Price, \$3.50.

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*Hæmorrhoids and Their Treatment.* The Varicose Syndrome of the Rectum. By KASPER BLOND, M.D., Vienna, Formerly First Assistant, Rothschild Hospital, Vienna; Hon. Consulting Surgeon, Municipal Hospital, Vienna, etc. Translated by E. STANLEY LEE, M.S., F.R.C.S., Hon. Assistant Surgeon, Westminster Hospital. Pp. 140; 49 illustrations, many in color. Baltimore: The Williams & Wilkins Company, 1940. Price, \$4.50.

#### NEW EDITIONS.

*The Practice of Medicine.* By JONATHAN CAMPBELL MEAKINS, M.D., LL.D., Professor of Medicine and Director of the Department of Medicine, McGill University; Physician-in-Chief, Royal Victoria Hospital, Montreal, etc. Pp. 1430; 516 illustrations (48 in color). Third Edition. St. Louis: The C. V. Mosby Company, 1940. Price, \$10.00.

"This volume is not intended for the specialist, nor does it aspire to be encyclopedic, but rather for the student and practitioner, to assist them in solving the numerous puzzles and problems with which they are daily confronted. So far as the patient is concerned, disease consists of symptoms. It is for these that he or she consults a physician. They represent the earliest manifestations of disease and therefore are of primary importance. They are the clues to the clinical riddles. For this reason they have been given particular prominence, and where possible their causation has been described and their significance has been pointed out. . . . I have diverted from the usual custom in textbooks on the practice of medicine and have inserted many illustrations with the hope that these may be more informative than a word description." (From the Author's Preface.) The author has been successful in including the chief advances of the 2 years that have elapsed since the publication of the second edition.

*Biochemistry for Medical Students.* By WILLIAM VEALE THORPE, M.A. (CANTAB.), PH.D. (LOND.), Reader in Chemical Physiology, University of Birmingham. Pp. 464; 37 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1940. Price, \$4.50.

*Rose and Careless Manual of Surgery.* American (Sixteenth) Edition. Edited by WILLIAM T. COUGHLIN, B.S., M.D., F.A.C.S., Professor of Surgery and Director of the Department of Surgery, St. Louis University School of Medicine; Surgeon-in-Chief, St. Mary's Group of Hospitals, St. Louis. From the Sixteenth English Edition by CECIL P. G. WAKELEY, D.Sc., F.R.C.S., F.R.S.E., F.R.S.A., F.A.C.S., F.R.A.C.S., Fellow of King's College, London; Senior Surgeon, King's College Hospital; Director of Surgical Studies and Lecturer in Surgery, King's College Hospital Medical School, etc., and JOHN B. HUNTER, M.C., M.CHIR. (CANTAB.), F.R.C.S. (ENG.), Surgeon, King's College Hospital; Lecturer in Surgery, King's College Hospital Medical School, etc. Pp. 1656; 1034 illustrations and 30 plates (some in color). Baltimore: The Williams & Wilkins Company, 1940. Price, \$9.00.

*The Treatment of Diabetes Mellitus.* By ELLIOTT P. JOSLIN, A.M., M.D., Sc.D., Medical Director, George F. Baker Clinic, New England Deaconess Hospital; Clinical Professor of Medicine Emeritus, Harvard Medical School, etc., HOWARD F. ROOT, M.D., Physician, New England Deaconess Hospital; Consultant in Medicine, Eastern Maine General Hospital, etc., PRISCILLA WHITE, M.D., Physician, New England Deaconess Hospital; Instructor in Pediatrics, Tufts College Medical School, and ALEXANDER MARBLE, A.M., M.D., Physician, New England Deaconess Hospital; Instructor in Medicine, Harvard Medical School. Pp. 783; illustrated. Seventh Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, \$7.50.

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*Practical Handbook of the Pathology of the Skin.* An Introduction to the Histology, Pathology, Bacteriology and Mycology of the Skin with Special Reference to Technique. By J. M. H. MACLEOD, M.A., M.D., F.R.C.P. (LOND.), Physician and Hon. Director of the Pathological Department, St. John's Hospital for Diseases of the Skin; Physician for Skin-Diseases to the Hospital for Tropical Diseases, London, etc., and I. MUENDE, M.B., B.S., B.Sc. (LOND.), Pathologist in charge of Out-Patients' Clinic and Lecturer in Pathology, St. John's Hospital for Diseases of the Skin; Dermatologist to the Middlesex County Council, Willesden General Hospital, etc. Pp. 415; 125 black and white and 27 colored illustrations. Second Edition. New York: Paul B. Hoeber, Inc., 1940. Price, \$9.00.

*Landmarks and Surface Markings of the Human Body.* By L. BATHE RAWLING, M.B., B.CH. (CANTAB.), F.R.C.S., Consulting Surgeon to St. Bartholomew's Hospital. Pp. 98; 36 illustrations. Eighth Edition (New Terminology). New York: Paul B. Hoeber, Inc., 1940. Price, \$3.00.

*Recent Advances in Endocrinology.* By A. T. CAMERON, M.A., D.Sc. (EDIN.), F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. Pp. 432; 67 illustrations including 3 plates. Fourth Edition. Philadelphia: The Blakiston Company, 1940. Price, \$5.00.

# PROGRESS OF MEDICAL SCIENCE

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## OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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## WEATHER AND THE CLIMATE.

THE importance of the effect of weather and the climate on the human being was recognized and described more than 2500 years ago by Hippocrates, the world's first meteorologist. It was he who insisted that basically all disease was due to interference with processes which currently are known as "oxidation," and that in the mechanism involved we were dealing with changes in the blood-vessels. This clinical observation 25 centuries ago is as true today as it was then.

In recent years the climatic factor, as expressed in terms of the season and the weather, has received the careful attention of a number of American and European investigators. Since the season and the weather function together as a constant environmental factor from the time a human being is conceived to the time he dies, the fact that they can be measured with a great deal of accuracy constitutes a distinct advantage. Of course, other environmental factors—diet, emotion, infection, fatigue and intoxication—influence an individual, but to evaluate them is often extremely difficult. Definite alterations, for example those involved in daily changes of temperature, are measurable, although there may not always be an absolutely uniform effect from meteorologic changes, since individual members of a community may protect themselves to different degrees. Not only can daily temperature changes be measured, but likewise barometric pressure, daily sunshine, daily precipitation and daily average wind velocity.

Every physiologic adjustment that is induced by weather alteration is apt to find reflection in any region of the body that is inadequate. This expresses itself either in unusual symptomatology, in change of function, or in actual lesions in the various organs of the body—factors that can be measured. Consequently, investigators have been able to measure not only the stimulus, *i. e.*, the weather, but also the effect of that stimulus upon the human being, *i. e.*, the clinical, biochemical and

vasomotor changes that are produced in the human being. Petersen<sup>9</sup> describes the vasomotor and biochemical changes that are induced in the population when a polar air mass passes over a population group. At first the capillaries are less permeable, the blood pressure is increased, the tissues are less hydrated, and the blood is relatively more alkaline ( $\text{CO}_2$  content decreased, blood pH increased). In general, this might be called a period of sympathicotonia which finds its reflection in the peripheral tissues, including the mucous membranes of the nose and throat. Gradually the vascular spasm is dissipated, the vessels become dilated to accommodate the increased demand of the organism for greater oxygen consumption, the blood pressure falls, the membranes become more permeable, and the tissues become relatively more acid and hydrated. At this time, presumably, the opportunity for bacterial penetration is greater.

In the field of contemporary otorhinolaryngologic studies, Podvinec<sup>11</sup> describes the climatic factors present in otolaryngology, while Amelung<sup>1</sup> shows the dependence of colds on climate and weather. A series of recent investigations by Sargent<sup>13a,b,c</sup> concerning the common cold and the weekly and seasonal trends of upper respiratory infections in a group of 2000 students indicate that in normal young men observed from day to day under normal conditions of activity and subject to the same meteorologic conditions, the initiation of a "cold" or "sore throat" is always seen to be preceded by an episode involving a fall in daily atmospheric temperature. The first stage of infection from the mucous membranes includes not only the presence of a suitable virus but the coincident biologic phase that makes penetration possible. The rôle of the weather in the etiology of a sudden epidemic of tonsillitis is discussed by Yamasaki.<sup>14</sup> Nineteen cases of acute tonsillitis in children, each child sufficiently ill to warrant hospitalization, are presented by Fabricant<sup>3a</sup> to illustrate the significance of the onset of the "cold front" in precipitating the disease. The precipitation of acute tonsillitis in children most often takes place in the wake of a "cold front," a time when the air temperature falls, the barometric pressure increases, and there is lessened humidity. At this time there is a change in the functional status of the mucous membranes of the nose and throat. A latent period or "lag" of a few hours to one or more days may occur before the actual initiation of the clinical symptoms.

The possibilities of experimental meteorobiologic research are illustrated by Preuner's<sup>12</sup> report of the effect of weather conditions on experimental asthma in guinea pigs. Reporting the results of allergic tests performed during the course of 5 years in a university clinic on 87 children presenting bronchial asthma or bronchus spasms, Becker<sup>2</sup> found that 25% of the children were susceptible to seasonal change or foggy weather. In a study of hay fever among the Japanese, Hara<sup>4</sup> emphasizes the rôle of the weather in precipitating the clinical symptoms. The nasal-bulbar route as a portal of entry for poliomyelitis is well known. Petersen and Mayne<sup>10</sup> believe that among the conditioning factors upon which individual susceptibility in poliomyelitis depends, the meteorologic situation plays an important rôle. The period of prodromal symptomatology is often initiated by the passage of a cold air mass, as is the final precipitation of the paralysis. Both a study of individual case records and the statistical evaluation of the non-epidemic

precipitation of cases in Chicago and of the New York epidemics of 1916 and 1931 make evident this association.

That there are seasonal variations in the incidence of acute purulent otitis media is maintained by Olaison.<sup>7</sup> The relationship between acute mastoiditis and the weather are discussed by both Kimura<sup>5</sup> and Fabricant.<sup>3b</sup> Lynch<sup>6</sup> finds that the greater prevalence of mastoiditis in the northern part of the United States is due to the cold climate which causes lowered resistance to the streptococcus and an increased virulence of that organism. Streptococci from different geographic regions and guinea pigs subjected to artificial climates typical of these regions were used by the author to find why the number of cases of mastoiditis increased steadily from the southern climes to the north. Peller, Stephenson and Souder<sup>8</sup> point out that in the United States Army and Navy the incidence of cutaneous and lip cancer had been found to be several times higher and that of internal cancer substantially lower, than for a comparable group in the civil population of such cities as New York, Chicago, London or Vienna. The authors conclude that the high frequency of cancer of the skin and lip and consequently the low frequency of internal cancer in the Army and Navy depend essentially on the exposure to dermatropic climatic conditions in childhood, adolescence and manhood. Exposure to actinic conditions during adolescence and youth seems more important in its effect on the frequency of surface cancer and the total cancer mortality than is exposure during manhood.

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## NEUROLOGY AND PSYCHIATRY.

UNDER THE CHARGE OF

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## EVALUATIONS OF PSYCHOANALYSIS.

It would seem appropriate at this time to review the attempts to estimate the permanent significance of the work of Freud. His death has given renewed impetus to these attempts at evaluation both for

therapy and for psychologic theory. Recent literature contains a number of interesting contributions which approach the issue by varied techniques and from varied perspectives.

The report of Kessel and Hyman,<sup>8</sup> with the subsequent additional report by Hyman,<sup>7</sup> consider the value of psychoanalysis as a therapeutic procedure as viewed by internists who refer patients from their general practice to specialists. In presenting their data they defined: *a*, the qualification for a psychoanalyst; *b*, a concept of what constitutes an analysis; and, *c*, a description of the type of clinical material referable to the psychoanalyst for the analysis. In *a*, a psychoanalyst should be a licensed physician who has had a general internship, has himself been analyzed and has completed two control analyses and has been accredited by the psychoanalytical society with which he is affiliated. In *b*, the analysis has required the attendance of the patient for hourly visits from 3 to 5 times a week over a period of time extending from 6 to 24 months and usually averaging 16 months. In *c*, clinical material consisted of patients suffering from frank psychoses such as schizophrenics, manic depressives, insanity and the symptomatic psychoses, patients with behavior problems and maladjustments, patients with simple neuroses such as anxiety and compulsion states and patients with visceral symptoms of a functional nature.

The final report summarizes the results as they were evaluated in 43 patients. Of these 43 patients, 15 suffered from profound psychiatric disease. Of these 15 treated, 12 were considered to be "dismal failures," 2 had results that were still questionable and 1 had a specific therapeutic triumph. Twenty-eight patients suffered psychiatric disorders of minor degree. Of these 28 patients, 17 were distinctly benefited. In 4 of the 17, the analytic cure could be applauded without reservation. In the remaining 13 of this group, improvement was definite but it was felt that the therapeutic result may possibly have been brought about or materially aided by alterations in the life situation apart from the analytical procedure. The remaining 11 patients experienced no significant benefit from their analysis. To recapitulate, of 43 patients treated, 23 were considered failures, 2 had outcomes of doubtful value, 5 were successes with unreserved endorsement of psychoanalysis as the therapeutic agent and 13 were successes with qualified endorsement of psychoanalysis.

Another approach to the problem is to be found in the report by Myerson<sup>10</sup> on the attitude of neurologists, psychiatrists, and psychologists toward psychoanalysis. A questionnaire was drawn up and sent to a group of leading psychologists connected with universities, to the officers and every third member of the American Neurological Association, to the officers and every tenth member of the American Psychiatric Association and more or less haphazardly a group of psychoanalysts were canvassed on the assumption that their membership in a psychoanalytical society necessitated only a small sample. The questionnaire asked the recipient to classify himself in one of four groups, namely:

1. Those individuals who completely accepted psychoanalysis.
2. Those who feel very favorably inclined towards it but do not wholly accept it and are to a certain extent skeptical.
3. Those who in the main tend to reject its tenets but feel that Freud has contributed indirectly to the human understanding.

4. Those who feel that his work has on the whole hindered the progress of the understanding of the mental diseases and the neuroses and reject him entirely.

Of 428 questionnaires sent, 307 individuals replied. Of the 97 members of the American Neurological Association who received questionnaires, 75 replied. These were grouped as follows: 5 belonged in Group 1; 8 classify themselves between 1 and 2; 23 stated they belong in Group 2; 4 classified themselves between Groups 2 and 3; 25 declared themselves to be in Group 3; 3 stated that between Groups 3 and 4 was a good enough allocation of their position; 4 totally rejected psychoanalysis and were hostile; 3 were definitely non-committal or equivocal.

Of the 266 members of the American Psychiatric Association canvassed on the basis stated above, 179 replied. Twenty-five classed themselves in Group 1; 15 between Groups 1 and 2; 54 in Group 2; 32 between Groups 2 and 3; 39 in Group 3 rejecting; 8 belong between this group and total rejection; while there was none who completely rejected psychoanalysis as without value. Six were non-committal.

Of the members of the American Psychoanalytic Association, 28 replies were received to 36 questionnaires sent. Of this group, 16 were in Group 1; 4 between Groups 1 and 2; 3 in Group 2; and 5 were skeptical or non-committal.

Of the miscellaneous group, made up mainly of important members of the American Psychological Association and some physiologists interested in psychologic research, 25 replies were received to 29 questionnaires sent. Two accepted psychoanalysis; 5 belonged in Group 2; 6 placed themselves between Groups 2 and 3; 7 placed themselves in Group 3; and 3 between Groups 3 and 4; 2 completely rejected and placed themselves in Group 4.

Thus, in this group of eminent men, having an almost 100 % inclusion in *Who's Who in Science and in America*, the general attitude is more on the rejection side than on the acceptance, and goes a little further in the direction indicated by the position of the American Neurological Association.

The author admitted that the questions were imperfect and did not permit of any complete answer. However, they did permit most writers to classify themselves somewhere in the 4 categories. In expanding his view concerning his own position, which was mainly in Group 3, he states that it is his belief that Freud was a great man, one of the great men of his time. The concrete values of his work appear to Myerson to be, in the main, indirect results of his work. By taking the obscenity out of sex and by emphasizing the struggle within the personality, he has made objective study possible and stimulated research into the human mind. Greater attention must be paid to the details of human life and the concealed human difficulties. Myerson rejects Freud's concept of the consciousness, the free-association technique, the doctrine of infantile sexuality and the whole concept of symbolism.

In a symposium under the title "Psychoanalysis as seen by Analyzed Psychologists," published in the *Journal of Abnormal and Social Psychology*, there is yet another attempt at evaluation of psychoanalysis. This symposium was inaugurated on the assumption that "analyzed"



experimental psychologists should be authoritative judges of psychoanalysis, since they have had training in scientific procedure as well as first-hand acquaintance with psychoanalysis in the rôle of analysand. The following psychologists have contributed to the symposium: Edwin G. Boring, Professor of Psychology, Harvard University; Carney Landis, Psychiatric Institute, Columbia University; J. F. Brown, University of Kansas; Raymond R. Willoughby, Brown University; Percival M. Symonds, Teachers College, Columbia University; Henry A. Murray, Harvard University Psychologic Clinic; Else Frenkel-Brunswik, Institute of Child Welfare, University of California; and David Shakow, Worcester State Hospital.

In addition, two psychoanalysts have contributed: Hanns Sachs, Boston, Mass., and Franz Alexander, Chicago Psychoanalytic Institute.

Following are brief summaries of the papers comprising the symposium:

Boring<sup>2</sup> gives a personal, somewhat autobiographic account of his analysis, the only one of the symposium which was undertaken for primarily therapeutic reasons. The analysis is therefore inevitably judged in terms of its therapeutic success; judged by that standard, it is pronounced a failure. Nevertheless, certain psychoanalytic phenomena which appeared during the course of the analysis are described: the feeling of sacrifice induced by the analysts' fees, the personal liking for the analyst (although the author does not admit that this was "transfer"), the recovery of old memories, the emotional upheavals during the analytic hour, the emotional reverberations after the analysis was terminated.

It is the author's belief that much of the relief derived from his own analysis was the result partly of a change in the situation which had been troubling him—a change which occurred without the influence of psychoanalysis. Beyond this relief, however, he can see little positive help obtained from the analysis. He concludes, in part: "Now, four years after the close of the analysis, I find myself quite uncertain as to whether it has made any important change in me. Too many other things have happened for me to say why I am as I am . . . . True, the analysis has had this advantage: having been analyzed, I can no longer feel that I have left any available stone unturned. But that would be a rather small return for so large an undertaking. . . . There is so much about this personality of mine that would be better if different, so much that analysis might have done and did not!"

Taking as his point of departure the paper by Boring, Sachs,<sup>14</sup> who served as Boring's analyst, considers the problem of how often a full cure can be achieved through analysis, and how the result compares with the necessary sacrifice of time, exertion, and money. He points out that in the case of Boring's analysis, the analysand presented no specific neurotic symptom; he presented rather a rigid, fully preserved personality structure, which was not receptive to a new way of living, or an entirely different type of emotional life. To attempt a fundamental change of character in this case did not seem advisable to the analyst; hence the "new personality" which the analysand sought was not forthcoming.

On one other point the author defends this analysis. He claims that the changed situation of which Boring speaks constituted a potential

trauma, which might have produced a breakdown, had not psychoanalysis been able to provide a stopgap.

Proceeding to a theoretical discussion of analysis, Sachs holds that a great obstacle to the correct appraisal of the therapeutic value of psychoanalysis is the absence of any objective standard concerning the following: 1, the seriousness and extent of the neurosis; 2, the strength of the forces opposing the therapy (primary and secondary gain, reality-situation, traumatic experiences, etc.); 3, the extent and duration of the therapeutic result. Despite its lacks, however, analysis seems to this analyst to be getting nearer the roots of psychologic problems than is any other current therapy, since it works on causation rather than the surface.

Starting with a statistical statement of his own analytic hours, Landis<sup>9</sup> proceeds to point out certain phenomena which occurred during the course of the analysis, and to explain them in the more usual terms of psychology.

1. *Anxiety.* The author became possessed by an anxiety which pervaded all his activities, in the course of the analysis. He holds that this resulted from the identity which he saw between the analyst and his (the author's) father; he compares his confessional with the analyst to his father's catechizing him for his misdeeds when he was a boy. Such a process following upon the discovery of identical situations has been called by psychologists emotional reintegration.

2. *Irritability.* This was explained as resulting from attempts to explain the author's actions, and the discovery that such attempts were irrational. Having been divested thus of his usual reference points for making decisions, he became irritable when forced to make choices.

3. *Transfer.* The feeling between analysand and analyst is described in this case as respect, rather than love. Again the phenomenon is explained on the basis of viewing the analyst in the father-rôle.

4. *Resistance.* Resistance became so marked after 200 hours of analysis that the analysis was temporarily discontinued. Upon resumption of analytic techniques the resistance was still present to such a marked extent that the analysis was finally discontinued permanently.

5. *Unconscious Memories.* Many forgotten events were recalled during analysis, but were again explained as resulting from the integrative process. Confronted with the specific task of mentally reconstructing the past in detail, the analysand is able to do so with unusual completeness.

6. *Dream Analysis.* Dreams were used as starting-points for free association. The analysand found most unusual in this connection his own ability to say unhesitatingly whether the analyst's interpretation of his dream were right or wrong, although he often blocked on giving the interpretation himself.

7. *Neurosis.* It is apparent that the analytic procedure can create a neurosis, as shown in the appearance of such symptoms as anxiety, apprehension, irritation, and resistance. With psychology attaching importance to the creation of "neuroses" in rats, it is time for psychoanalysts to step forward and say plainly that they know how to set up a neurosis in human beings.

Some attention is given to the psychology of the analysts, which the author says lies in the fact that they have something important to say

but no language in which to say it. Since they must stick to analytic jargon, they acquire no technical vocabulary, no technique of scientific reporting.

It is concluded that the psychoanalytic phenomena are as much the result of the particular method used as of the basic personality structure.

Brown<sup>3</sup> submits that psychoanalysis embraces three different fields of endeavor, which must be evaluated separately: 1, a method of psychologic observation (free association, dream analysis, transference); 2, a systematized set of theoretical constructs, to order the psychologic data found by this method; and 3, a method of psychotherapy in which techniques are used in a special sense to change the structure of the human personality.

Much confusion has resulted from the fact that critics attempt to draw implications from one field to another when such conclusions do not follow.

On the basis of his own analysis, the author draws the following conclusions: 1, granted that the rôle of unconscious motivational processes is important in determining human behavior, psychoanalysis is a uniquely successful way of studying them; 2, granted the necessity for theoretical conceptions in systematic science, those of psychoanalysis are the most adequate we have in accounting for the sources and destruction of energy in the integrated behavior of the organism as a whole; 3, when one keeps in mind the difficulties which confront all psychotherapy and also the ambitiousness of psychoanalytic therapy, psychoanalysis has been unquestionably successful with certain types of mental disorder.

Willoughby<sup>17</sup> attempts to reduce psychoanalytic procedures to the operational basis which has become popular in psychology. The author contends that psychoanalysis has made the most impressive observations on affective phenomena in existence: 1, the emphasis on concept of drive; 2, the concept of conflict among drives, now being explored by experimental psychoanalysis; 3, the reaction of the individual when one drive inhibits the expression of another; and 4, the return of an inhibited drive to motor expression when the inhibition is relaxed.

The two phenomena of interpretation and transference are then put on a psychologic basis. It is argued that the basic process in interpretation is identical with problem-solving; more particularly, with sudden insight which occasionally obtains in problem-solving activities. It is likewise argued that transference is reducible to the proposition that similar stimuli evoke similar reactions; the theory of generalization in learning may suffice to explain psychoanalytic transfer.

The author's attitude toward psychoanalysis may be summed up in his own words: ". . . there is no such 'thing' as 'psychoanalysis.' There is a subject, in the emotional stress engendered by conflicting habit patterns, largely implicit; there is a psychologist, accustomed to think about such topics as learning and frustration, and having a knowledge of and if possible some actual experience with re-educative procedures; and there is an experimental situation, consisting mostly of freedom from irrelevant stimulation. It will not be surprising if from the repeated concurrence of these elements therapeutic habits and formulations arise having some relationship to those that have arisen from similar situations engaged in by psychoanalysts—or teachers, or priests."

Symonds<sup>16</sup> is anxious again to emphasize the difference between psychoanalytic theory and the process of psychoanalysis. Deductions made on the basis of a single analysis, as applicable to a single case, are not so open to question as those made from psychoanalytic theory, as applicable to human being in general.

Since psychoanalysis is concerned with the conflicts within the individual himself, it seems to be a prerequisite to successful education in children. The child cannot be expected to adjust himself in school if he is not relatively free from inner conflicts. Moreover, many of his conflicts are results of attitudes of other persons with whom he is associated. Therefore, it seems clear that many teachers and parents need psychoanalysis, as well as many children.

Such a program is clearly impractical; therefore it becomes necessary for psychologic research to attempt to discover short cuts in the resolution of conflicts. The author points out certain attempts in this direction which have already been made—notably the use of projective techniques in the study of children's problems. For use with adults, group methods seem promising. “. . . the developments of both psychology and psychoanalysis have been drawing more closely together in interest, outlook, and formulation; and now with comparative suddenness psychologists everywhere are ready to embrace psychoanalysis, to put it to rigorous experimental tests, and to determine exactly what it contains of value to be incorporated into psychological theory.”

Murray<sup>12</sup> gives an autobiographic sketch of the author's student days, illustrating his shifts from medicine to psychoanalysis, and ending with a summary of the major psychoanalytic concepts, all told in most amazingly literary style, which must be read to be appreciated. He summarizes, with a possible analytic preference, such concepts as drive, sex, aggression, ego, ego ideal, superego, castration, regression, infantile determination, sublimation. Yet he flays those psychoanalysts who persist in making of their science a cult, pleading constantly for a more closely-knit, esoteric organization. His own suggestion for widening the psychoanalytic structure is a graduate institute of psychology providing education in anatomy, physiology, neurology, scientific method and statistics, clinical psychology and psychoanalysis, general psychology and its special branches, sociology, and anthropology. He quotes Freud as saying that the rightful place of psychoanalysis is with psychology, and upholds him in this feeling.

He concludes with a condemnation of the superficiality that has come to characterize modern American culture—a superficiality which he finds expressed in the attack of psychiatry upon its problems, as well as in psychology. “In contrast to all this shallowness,” he says, “there is psychoanalysis, offering its corrective way; and for what it can do here, if for no other reason, I trumpet out its virtues.”

Frenkel-Brunswik<sup>6</sup> goes farthest of any in the symposium in attempting to reconcile psychoanalysis with her own system of personality theory. She differentiates, as does her husband, Egon Brunswik, between “central” and “peripheral” layers in personality. The former is the level of overt reaction; the latter, the level of inner forces guiding human conduct. The latter is the more essential part of personality, but study of it has been handicapped because of the difficulty of gaining access to the “central” layers of personality. She makes a second distinction between the immediate effects of peripheral behavior in the

environment, which she calls "proximal," and the more remote results of the individual's activities, which are labelled "distal."

Proceeding from this theoretical framework, Brunswik argues that the major contribution of psychoanalysis is in its provision of an instrument which can be used as a probe into the central portion of the personality. She emphasizes, however, that psychoanalysis begins with the peripheral region, extrapolating from proximal material to the deeper, central material. She, too, emphasizes the importance of projective techniques in getting at the central factors in personality. Examples are given, some from the Adolescent Study at Berkeley, of the application of "central" methods to problems of personality.

Brunswik concludes with a healthy warning against the use of psychoanalysis to get at central factors, with no empirical check on their validity. ". . . psychological intuitions and interpretations have to be checked back to the mass of surface data. Unless this is done, the data remain without empirical meaning. All the more does this statement hold true for psychoanalysis. The Ego should remain the subject matter of psychology, and extrapolations should be used chiefly in order to throw light back upon the surface phenomena of behavior and achievement. In thus returning ultimately to the surface region, we will have attempted a deep psychology of the surface, rather than indulged in a superficial psychology of the depth."

Shakow<sup>15</sup> became favorably impressed by the psychoanalysts not so much because of what the analysts had to offer, as because of how little the others in the field seemed to offer. At least psychoanalysis presented always for a given patient some hypothesis with which to work. Hence, analysis was undertaken in an attempt to gain some objective basis for evaluating psychoanalysis as therapy. Free association, dream analysis, interpretation, resistance, and transference are described as they were experienced in the analytic sessions.

Shakow interprets analysis as an experiment upon one subject on whom many repeated sessions are available (analogous perhaps to running a single rat through a maze 300 times). It differs from the laboratory experiment, however, in that the analyst takes whatever data comes to hand during the analytic session, while the experimentalist selects his materials beforehand, experimenting on one aspect only of the situation.

From a purely personal point of view, the author feels that he has improved as a person and as a psychologist as the result of his analysis. He is particularly impressed with the sensitization to the great amount of mental activity which goes on beneath the surface, which has resulted from his analysis. He argues also that psychoanalysis offers leads for investigation to the experimentally inclined person. He concludes, "It would seem that the above account indicates almost all profit. For most psychologists I believe this conclusion to be valid if the investment of time and money required is not excessive."

Alexander<sup>1</sup> concludes the symposium with a summarizing statement which is somewhat in the nature of a rebuttal. He thanks the psychologists for their verdict of "not guilty," but interprets that verdict as essentially an act of mercy. "Psychoanalysis is a bad boy but very able, and there is some hope for his improvement."

He argues that psychoanalysis has contributed to a basic issue in psychology: it has developed a method which is adjusted to the nature

of the field of investigation, the human personality. He accuses experimental psychologists of losing sight of the real scope of their field, and of applying experimental methods to inconsequential details within the field of psychology. He points to such theorists as Kurt Lewin and Henry A. Murray as recognizing finally the value of psychoanalysis in psychologic theory, and calls upon the experimental psychologists to examine the Freudian concepts in the psychologic laboratory.

Other experimental psychologists are already at work. Child<sup>4</sup> reports on the relation between measures of infantile amnesia and of neuroticism. Diven<sup>5</sup> has investigated certain determinants in the conditioning of anxiety reaction. Mowrer<sup>11</sup> has investigated the Freudian concept of regression as contingent upon the two factors of fixation and frustration. His experiments were conducted with animals and consequently the behavior reported was considered merely as an analogue of human regression. Rosenzweig<sup>13</sup> has investigated experimentally the concept of repression. In the field of psychosomatic medicine, physiologists are equally active in investigating psychoanalytical concepts. By the application of the principles of the scientific method in the associated areas of interest, the evaluation of psychoanalysis in the field of medicine will properly proceed.

GEORGE S. JOHNSON, M.D.

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#### PHYSIOLOGY

PROCEEDINGS OF  
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA  
SESSION OF OCTOBER 15, 1940

**Locus and Nature of Crossed Inhibition in the Spinal Monkey.**  
GRAYSON P. MCCOUCH, JOSEPH HUGHES, and WINIFRED B. STEWART  
(Department of Physiology, University of Pennsylvania School of Medicine, and Pennsylvania Hospital for Mental and Nervous Diseases).  
In spinal cats and dogs crossed inhibition of the ipsilateral flexor reflex is associated with inhibition of the internuncial cord potential of equivalent degree. In the chronically spinal macaque monkey, on the other hand, a crossed afferent volley confined to alpha, beta, and gamma fibers may markedly inhibit the reflex without modifying the internuncial potential. Stronger crossed stimuli may reduce the internuncial potential to lesser or equal degree than the reduction of the reflex response. With suitable grading of inhibitory and excitatory volleys, the crossed component of the internuncial potential from the excitatory

volley proves to be more susceptible to inhibition than the ipsilateral component.

The case in which reflex inhibition occurs without demonstrable change in internuncial potential is of interest in relation to current theories of inhibition. Such theories may be divided into those which refer the reduction in irritability to immediately precedent response of the same units and those which invoke specific inhibitory endings. If such records may be accepted as evidence that excitatory drive upon the motoneurons is not essentially altered, then inhibition has occurred in them in the absence of immediately preceding activity.

**The Effect of Bromide Administered to Pregnant Rats on the Learning Ability of the Offspring.** B. K. HARNED, H. C. HAMILTON, and J. C. BORRUS (Department of Pharmacology, Woman's Medical College of Pennsylvania, and the Department of Psychology, Temple University). The learning ability of rats born of normal pregnancies was compared with that of siblings born from mothers administered sodium bromide from the fourth through the twelfth day of gestation. The drug was administered in the drinking water and the total amount averaged 192 mg./kilo. The maximal depression produced in the mothers did not exceed a mild apathy.

Analyses of 4-hour-old newborn rats disclosed an average sodium bromide content of 75 mg./kilo. At 21 days of age the animals were weaned and until 40 days of age they were kept on a diet containing 1% of sodium chloride. At the end of this period the average sodium bromide excretion per rat per 24 hours was 1.6 micrograms.

The learning tests, made in a five cul-de-sac maze with the correct pathway consisting of rrlr turns, were started at 60 days of age and after 3 preliminary trials continued 50 days at the rate of one test per day. Errors made and time consumed served as the criteria for learning. There were 23 control and 29 experimental animals with approximately the same distribution of the sexes in the two groups. For the 50 trials the mean number of errors made by the control group was 146 and for the experimental group 178 and the chances that the difference is significant are 94 per 100. The mean time required by the control group for the 50 trials was 1099 seconds and by the experimental group 1701 seconds and the chances that this difference is significant are 96 per 100. The variability of the experimental group was greater than that of the control group in both errors and time. For both criteria the chances are 99 per 100 that the differences between their sigmas are real.

These results suggest that the administration of relatively small amounts of sodium bromide to pregnant rats decreases the learning ability of the offspring.

**Studies in Capillary Mobility, Minute Vessel Pressure, and Cutaneous Lymphatic Flow in Arterial Hypertension.** R. B. RUTHERFORD, J. Q. GRIFFITH, JR., E. ROBERTS, H. O'B. CORBIT, and M. A. LINDAUER (Robinette Foundation, Hospital of the University of Pennsylvania). Counts of cutaneous capillaries were made in normal subjects, in persons with cardiovascular disease without hypertension, and patients with cardiovascular disease with hypertension. Initial counts were compared with total counts made in the area of a histamine flare. While in many instances there was no difference in the response of

persons with cardiovascular disease and normal subjects, there was a tendency in certain cases of the former for initial counts to equal or approximate total counts after histamine. This was regarded as representing a diminished capillary mobility.

Minute vessel pressure was measured by an indirect technique evolved from the Danzer Hooker method and thought to have certain advantages over it. It is probable that the pressure read is that in the pre-capillary arteriole, not that in the capillary. The normal range is from 13 to 23 mm. of mercury, most readings lying between 15 and 20. In the flare area of a histamine wheal there is, in the normal subject, a rise of 3 mm. or more. In subjects with hypertension the minute vessel pressure may be normal or increased. After histamine it may rise normally, or the rise may be exaggerated, or there may be no significant change. Patients with diminished capillary mobility frequently show no significant rise in pressure after histamine.

Cutaneous lymphatic flow was measured in normal and hypertensive subjects by the dye method of McMaster. In hypertensive subjects it was found to be either normal or increased. Increased flow was frequently but not invariably associated with increased minute vessel pressure.

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**Quantitative Studies on the Passage of Protein Molecules Through the Glomerular Membranes.** P. A. BOTT and A. N. RICHARDS (Laboratory of Pharmacology, University of Pennsylvania). Since normal glomerular membranes in amphibia have been shown to be completely permeable to inulin (molecular weight 5100) and impermeable to serum albumin (molecular weight approximately 70,000), an attempt was made to obtain more definite knowledge as to the nature and limit of permeability of the glomerular membranes by studying the passage through them of proteins with molecular weights between those two. The experiments were of two types: 1, "Direct" experiments (chiefly on Necturi) in which fluid collected from Bowman's capsule was analyzed for protein. Collections were made while kidneys were being perfused with known protein solutions. 2, "Indirect" experiments (chiefly on frogs) in which urine collected from the ureters during perfusion of protein and inulin was analyzed for these two substances, the inulin concentration ratio then being used to calculate the concentration of protein in glomerular fluid.

The protein concentration of glomerular fluid expressed as per cent of that found in perfusion fluid averaged as follows: crystalline hen's egg albumin 57, crystalline duck egg albumin 55, crystalline lactoglobulin 80, and the purified protein derivative "P.P.D." from tuberculin 86 (also, based on fewer experiments: Bence-Jones protein 36 and insulin 25). The tuberculin protein has a molecular weight of about 13,500 while all the others have been regarded as members of the 35,200 molecular weight group. The results of the direct and indirect methods when used with the same protein, agree sufficiently well to exclude the possibility that tubular reabsorption influences results of "indirect" experiments. There was no indication of an increased permeability due to passage of these proteins through the membranes except, possibly, in the case of insulin. Urethane in a concentration of 7% increased permeability.

It is suggested that while filtrability of the proteins may be grossly a matter of size, factors other than size play a part.



**Effect of Pantothenic Acid on Growth and Reproduction of Rats on Synthetic Diets.** KLAUS UNNA (Merck Institute for Therapeutic Research, Rahway, N. J.). In these studies rats were maintained on a basal diet consisting of vitamin free casein, 18%; dextrose (cerelose), 68%; crisco, 9%; salt mixture No. 1 U.S.P. XI, 4%; and cod-liver oil, 2%, and supplemented daily with 40 micrograms each of thiamin, riboflavin and pyridoxine, 0.5 mg. of nicotinic amide and 5 mg. of choline chloride. A dose of 3 mg. of alpha tocopherol was given once weekly. Unless pantothenic acid is supplied, the rats cease to grow after 4 weeks on this diet, and die within 6 to 10 weeks. The pantothenic acid deficient rats exhibit external symptoms principally noticeable in the change of the condition of the fur coat. If pantothenic acid is supplied in daily doses from 10 to 200 micrograms a graded dose response is obtained in these animals. Daily doses of 100 micrograms meet the growth requirement of the rats on this diet and prevent the appearance of deficiency symptoms. The growth response to a liver preparation supplying adequate amounts of pantothenic acid is greater than that obtained with pantothenic acid alone. This would indicate the presence of unknown and yet unidentified factors in liver. With 10 or 25 micrograms of pantothenic acid daily the animals reached stationary weights. With larger doses growth was continuous and these animals reached maturity. Our first attempt to mate animals receiving 75, 100, 200 micrograms were successful insofar as two litters, one of 7 and one of 5, of normal birth-weight were obtained. These young rats, however, did not gain rapidly in weight in spite of the fact that they were nursed by their mothers. This might be taken as a further indication of the necessity of some other factor supplied in natural food-stuffs, such as liver. Our results show that the incorporation of adequate amounts of thiamin, riboflavin, nicotinic amide, B<sub>6</sub> and pantothenic acid into a synthetic diet free from water soluble vitamins assures continuous growth until maturity and reproduction.

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